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CONGENITAL CLEFTS OF THE FACE AND JAWS

A SURVEY OF THREE HUNDRED AND FIFTY CASES IN WHICH OPERATION WAS PERFORMED

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The charts and records of 350 cases of harelip and cleft palate have been reviewed. These cases were selected because, with the exception of 4 which were added to make an even number, the data are recorded by the classification and plan (figs. 1 and 2) suggested a number of years ago by Dr. John Staige Davis and myself.

This classification is based on a series of congenital clefts which involve the face and jaw. The condition of the alveolar process, i. e., whether it is normal or cleft, is emphasized to the point that it is the deciding factor in describing the cases. Three main groups naturally follow: Group I, prealveolar cleft; Group II, postalveolar cleft, and Group III, alveolar cleft. Thus new terms of description are evolved to designate the case as a whole.

The objection to such a plan is concisely stated in the comment of a great medical editor, to wit: "Special terms in special fields tend toward confusion and misunderstanding to the general reader, and should be erased in favor of terms of common usage." This is a most valid objection. However, the common terms of harelip and cleft palate are so general in their meaning as to the conditions present in a given case, and although adjectives—single, double, complete and incomplete—are added, the effort to be more specific in description appears to have some merit. I hope that the worth of the plan may be demonstrated throughout the survey. The charts contain accumulated data on several phases of the problem of harelip and cleft palate. In order to abstract them as clearly as possible, the report is divided into four parts:

I. Familial Incidence and Associated Deformities and Conditions
II. Combination and Degree of the Clefts; Age for and Sequence of Repair
III. Operative Result and Technic Used
IV. Conclusions

I. FAMILIAL INCIDENCE AND ASSOCIATED DEFORMITIES AND CONDITIONS

One of the most interesting problems in the field of harelip and cleft palate is that of etiology. On the obverse side of the chart used is the social history, divided to be specific, of the father, the mother

CONGENITAL CLEFT LIP AND PALATE

HISTORY

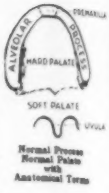
Normal Lip with Anatomical Terms

General No. ..... Date ..... Surgical No. .....

Name .....

Address ..... Date of birth .....

Sex ..... Color .....



Normal Process Normal Palate with Anatomical Terms

FATHER. Name .....
Age ..... Nationality .....
Occupation .....
Habits .....
Mentality .....
Health at time of impregnation .....
Wassermann .....

MOTHER. Age ..... Nationality .....
Occupation .....
Habits .....
Mentality .....
Health at time of conception .....
and for 2½ months thereafter .....
Excessive vomiting .....
Injury during first 2½ months of pregnancy .....
Maternal impressions .....
Time of occurrence .....
Wassermann .....

CHILD. Legitimate ..... or illegitimate .....
Whether first child .....
Other congenital clefts in the family? .....
Relationship ..... Location .....
Extent .....
Birth. Normal ..... Complicated .....
General condition .....
Preliminary care .....
Wassermann .....

PHYSICAL EXAMINATION.

Head ..... Teeth .....
Tonsils ..... Adenoids .....
Chest .....
Abdomen .....
Extremities .....
Other congenital deformities .....

LABORATORY EXAMINATIONS.

BLOOD. Hemoglobin ..... Clotting time .....
URINE. Acetone ..... Diacetic acid .....
Albumin ..... Sugar .....
SPECIAL EXAMINATIONS.

Fig. 1.—Obverse side of the chart reduced from the hospital size of 11 by 8 inches. The data are discussed in the text, with the observations that two items only are of importance, viz., familial incidence and associated deformities. However, the plan of separate notes for the parents and the child offers an orderly, concise and comprehensive questionnaire on social history.

Lip Column

SPECIAL EXAMINATION

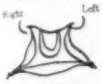
Process and Palate Column

GROUP I. PRE-ALVEOLAR (Process) CLEFT. (Lip cleft. Process normal).

1. **Unilateral.** Right { Complete (Cleft extends into nostril) ..... / Incomplete (Does not extend into nostril) .....
   Left { Complete ..... / Incomplete .....
2. **Median** (rare) Complete..... Incomplete.....
3. **Bilateral.** Right { Complete..... / Incomplete..... Left { Complete ..... / Incomplete.....

Describe nostrils.....

NOTE: If associated with palate cleft, also fill in GROUP II form.



GROUP II. POST-ALVEOLAR (Process) CLEFT. (Palate cleft. Process normal).

1. Soft Palate..... Extent in thirds.....
2. Hard Palate..... Extent in thirds.....

Situation and attachment of septum.....

Measurement of widest portion of cleft.....

Palatine arch..... High..... Low.....

NOTE. If associated with lip cleft, fill in GROUP I form.

GROUP III. ALVEOLAR (Process) CLEFT. (Follows incisor sutures).

1. **Unilateral.**

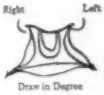
PROCESS. Right { Complete (Cleft extends through alveolar process) ..... / Incomplete (Cleft does not extend entirely through process) .....
Left { Complete ..... / Incomplete .....

PALATE. Unilateral..... Bilateral..... Median.....
Complete..... Incomplete.....
Palatine arch..... High..... Low.....

LIP. Unilateral..... Bilateral..... Median.....
Complete..... Incomplete.....

Measure Process Cleft
Measure Palate Cleft
Draw in Degree

2. **Median** (rare). Complete..... Incomplete.....



3. **Bilateral.**

PROCESS. Right { Complete ..... / Incomplete..... Left { Complete..... / Incomplete.....
PALATE. Right { Complete ..... / Incomplete ..... Left { Complete..... / Incomplete.....
Palatine arch..... High..... Low.....
LIP. Right { Complete..... / Incomplete..... Left { Complete..... / Incomplete.....

Measure Process Clefts
Measure Palate Clefts
Draw in Degree

Locate any rudimentary structure.....

Note projection of premaxilla.....

Note rotation of premaxilla.....

Situation and attachment of nasal septum.....

Measurement of cleft at alveolar process.....

Measurement of widest portion of palate cleft.....

.....

If previous operations performed elsewhere, give dates.

Fill in original condition on proper group form.

Impression.....

Recommendation.....

Photographs. Date..... No.....
Date..... No.....

X-ray plates. Date..... No.....
Date..... No.....

Palate casts. Date..... No.....

Phonographic speech records.
Date..... No.....
Date..... No.....

Fig. 2.—The reduced reverse side of the chart, with plans for graphic, literal record of the case as a whole. In Group I diagrams appear in the lip column only, so that no case with a cleft of the alveolar process and hard and soft palates can be placed in this group. In Group II there are no diagrams in the lip column. There is a normal alveolar process on the diagram in the palate column. In Group III there are diagrams in both lip and palate columns, because in this group all clefts appear except in cases in which there were normal hard and soft palates, in which instance the outlines pertaining to the lip and process are marked and the outline pertaining to the palate is crossed out.

and the child (fig. 1), which is recorded in the effort to collect data which may bear on the question of cause.

Neither the ages of the parents nor the disparity of ages between the father and the mother apparently have any bearing on the problem. A record was made of nationalities and consequent cross-breeds. It is interesting to note the many strains that go to make up the American citizen, but I cannot interpret these as having a bearing on the subject.

TABLE 1.—*Records of Cases with Familial Incidence*

Case	Patient	Group	Member of Family Affected
1	L. A.	III B.	Mother, cleft lip
2	K. F.	II-2/3	Father, identical cleft
3	R. S.	III L.C.	Uncle, cleft lip
4	L. H.	III L.C.	Brother, cleft lip, right
5	R. S.	III B.	Brother, cleft lip, right
6	E. H.	III L.C.	Maternal uncle, cleft lip
7	W. F.	III B.	Cousin, both lip and palate clefts
8	J. D. N.	III B.	Paternal great uncle, cleft unknown
9	D. K.	III L.C.	Sister, complete cleft lip and palate, left
10	D. A.	III, with normal palate	Father, cleft lip and palate
11	F. J.	III L.C.	Sister, identical cleft
12	S. H.	II-2/3	Maternal grandmother, cleft palate
13	A. H.	II-2/3	Sister, cleft palate
14	T. H.	II-2/3	Sister, cleft palate
15	S. H.	II, soft palate only	Father, complete cleft
16	J. W.	III L.C.	Is a twin; sister normal
17	G. H.	III, with normal palate	One brother and one sister with clefts; no record of form
18	A. R.	III L.C.	Brother, Group III
19	L. N.	III R.C.	Mother, III L.C.
20	L. B.	III R.C.	Cousin of father; no form recorded
21	G. D.	III L.C.	Cousin of father; no form recorded
22	A. F.	III L.C.	Paternal aunt; no form recorded
23	J. R.	I L.	Maternal uncle; no form recorded
24	F. R.	III B.	Two brothers, each in Group I
25	H. K.	II-2/3	Cousin, Group II
26	R. T.	III R.C.	Cousin on maternal side, Group III
27	C. G.	III B.	Father, Group I R.
28	H. H.	III L.C.	Aunt, III B.
29	M. T.	III L., with normal palate	One brother, III B.
30	G. S.	III B.	Three brothers: Peter, I R.; Mike, III L.C.; Ed, I L.
31	R. P.	III L.C.	One brother, Group III
32	J. C.	III B.	One brother, III L.C.; father's cousin, lip and palate clefts
33	A. D.	III B.	One brother, Group II
34	E. C.	I R.	Twin; sister normal

A study of the mentality of the father and the mother was also made. This interpretation is most elusive, and while it is not uncommon to encounter mothers or fathers who are exacting and suspicious, and some that may be loosely described as morons, on the other hand there are many of a high degree of intelligence. There was only 1 case in which there was a history of gross mental disorder.

Wassermann tests were not done as a routine measure, but were made occasionally when syphilis was suspected. There is a record of only 1 case of syphilis, and that was in the mother. The history of the mother showed some evidence that nausea and vomiting were present in the early months of pregnancy.

Questions as to maternal impressions so infrequently evoked a positive response that the few cases cited can have no value. In fact, most parents had never heard of the condition.

The first item of possible value in the study of etiology is the familial incidence, concerning which there are several interesting stories. The cases in which there was a familial incidence are presented in detail in table 1. The groups are described in the tables in the text as follows: III B., Group III, bilateral; II–2/3, Group II, two thirds of hard palate affected; III L. C., Group III, left complete, etc.

In the series of 350 cases, there were 34, or 9.2 per cent, with a history of familial incidence. When one remembers that few families

Fig. 3.—A set of twins; the boy is normal, and the girl has all the clefts on one side.

are acquainted with their history, other than that of members with whom they are in immediate contact, the percentage may be really large.

In case 30, the child had a double harelip and palate and was the fourth child in sequence with a cleft. I repaired the cleft of the three brothers. This is the only case of this kind in the series.

In the two sets of twins, in both cases apparently not identical, one child had a cleft (fig. 3) and the other child was normal. In another set, one child had a double harelip and the other one was normal, while in a pair of true identical twins (not in this series) both had the same series of clefts, but reversed.

Two sisters with Group II clefts had palates apparently from the same mold.

A father, 40 years of age, had a Group II cleft which had never been repaired, and when his daughter was seen it was quite startling to find that they had identical clefts.

In 26 of the cases there were associated deformities and other conditions (table 2). The 8 with hernia are not of great significance. Examination for thymus was not made as a routine; in fact, it was made quite infrequently after negative roentgenograms had been obtained several times. The unexplained death reported in the mortality statistics may well have been caused by the presence of an enlarged thymus. The case of multiple clefts of the face and jaw (fig. 4) in my

TABLE 2.—*Cases with Associated Deformities and Other Conditions*

Case	Patient	Group	Associated Deformity and Conditions
1	V. C.	III B., with no mesial segments in the process	Umbilical hernia
2	N. S.	I R.	Large birth mark on left hand
3	R. L.	III L.C.	Right inguinal hernia
4	F. C.	III B.	Mongolian
5	T. C.	II-1/3	Mentally defective; hydrocephalic (Spears)
6	R. D.	III L.C.	Subnormal with big head
7	J. H.	III L.C.	Left hydrocele
8	J. T.	III R.C.	Congenital deformity of right hand
9	D. G.	III R.C.	Cleft at each angle of mouth; coloboma of eyelid; dermoid of eyeball; subnormal
10	D. P.	III L.C.	Subnormal
11	L. H.	III B.	Subnormal
12	R. N.	II	Mongolian
13	J. W.	III R.C.	Indirect inguinal hernia
14	K. C.	III L.C.	Right inguinal hernia
15	B. S.	II-1/3	Umbilical hernia
16	H. D.	III B.	Extra thumb on right hand
17	G. K.	III B.	Equinovalgus; absence of left thumb
18	E. J.	I L.	Enlarged thymus
19	W. S.	III R.C.	Right inguinal hernia
20	R. J.	III R.C.	Mentally subnormal
21	L. O.	II-2/3	Enlarged thymus
22	H. B.	III R., with normal palate	Penile hypospadias; brother with spina bifida
23	M. B.	I L.	Eczema and enlarged thymus
24	B. N.	III B.	Undescended testicle
25	C. K.	II-2/3 soft	Umbilical and right inguinal hernia
26	L. W.	III R.C.	Umbilical hernia

series is one which, along with the reports of others collected from the literature, indicates the many possibilities of failure in embryonal growth and supports the statement that harelip and cleft palate are only a part of a group of congenital deformities in this area.

The phase of the problem of congenital clefts of the face and jaw which has a moral tinge is the question of operation on the mentally defective. There were 2 mongolians in my series. The mongolian child is usually active and vigorous physically, and it appears proper to repair the clefts of such a child. The more severe cases of mental defect present a great problem. There were 3 children who showed severe mental defect, but in each instance I was greatly influenced by the desire of the sorrowing parents, and the clefts were repaired. The various other deformities and conditions are reported as a matter of record.

The 34 cases with familial incidence and the 26 cases with associated deformities and conditions total 60, or 17.1 per cent of the total number of cases.

I have no particular comment to make. The survey of this part of the subject is offered in the hope that the reader may find some points of interest bearing on this phase of the problem of harelip and cleft palate.

II. COMBINATION AND DEGREE OF THE CLEFTS; AGE FOR AND SEQUENCE OF OPERATION

This part of the survey deals with the case as a whole, the data bearing on this phase of the subject being recorded on the reverse side of the chart (fig. 2). The diagrams on the chart are illustrated in the text by typical cases. The groups are studied separately.

Fig. 4.—A child with multiple clefts of the face and jaw. The cleft in the body of the lip is due to failure of the right maxillary division to unite with the frontonasal division. The clefts at the right and left angles of the mouth are due to the failure of the right and left mandibular divisions to unite with the right and left maxillary divisions, so that three breaks appear in the encircling musculature of the mouth. The muscle elements of the right maxillary division are out of contact on both sides and appear as a rounded, humped-up ball of contractile tissue. The several clefts were repaired on the same principle of muscle repair, which apparently fits the cleft at the angles as well as that in the body of the lip.

Group I. Prealveolar Process Cleft (fig. 5).—In this group, the alveolar process and the hard and soft palates are normal. The defect is that of a cleft in front of a normal alveolar process. The statistics on this combination are as follows:

	Cases	F.	M.
Right cleft (fig. 5*A*)	11	9	2
Left cleft (fig. 5*B*)	26	10	16
Bilateral cleft (fig. 5*C*)	1	1	0
Total	38	20	18

The degree of the cleft may vary from simple notches at the vermilion border and lines on the skin, etc., to more severe clefts, but in none of the cases has the floor of the nostril been involved. These are the incomplete harelips. I have yet to see a complete harelip without a cleft of the alveolar process. In all of the cases there was some muscle contact in the lip, although this feature may be slight. The nostrils are usually well alined, yet it is possible to have a case in which the ala is pulled aside.

The age for operation in group I is within the judgment of the operator and depends on the circumstance of convenience, health of the child, etc. There is no hurry from the surgical standpoint because the tissues of the lip develop along with the body (fig. 9). The babies nurse normally, and the operation in many cases is postponed until they

Fig. 5.—Group I, prealveolar cleft: *A*, right; *B*, left; *C*, bilateral.

are weaned. It is just as wise to perform the operation early and then put the child back on the breast. It is a fair statement to say that the operation may be performed any time after feeding is established and the baby is gaining weight.

Group II. Postalveolar Process Cleft (fig. 6).—In this group the lip and the alveolar process are normally united. The hard and the soft palate are cleft in varying degrees. There is one definite, constant similarity; the clefts are always symmetrical. They differ in the anterior posterior extent and in the width measured at the junction of the hard and the soft palate. There is equal tissue on either side, except in an occasional case in which I have noted an apparent disparity in the soft palate. It is apparent and not real, because in the denudation and suture it is possible to make an even approximation.

It is not easy to illustrate the various degrees of clefts, so a photograph of an 8 year old boy with a II–2/3 combination is shown, supplemented by a copy of the diagram from the chart (fig. 6).

The statistics in this group are as follows, it being understood, of course, that whenever the hard palate is involved, the soft palate is completely cleft:

Degree of Cleft		Cases	F.	M.
Hard palate	3/3	11	7	4
	2/3	22	17	5
	1/3	6	5	12
Soft palate only		6	4	2
Total		56	33	23

In Group II the question of the use of direct force to assist in closing the cleft has never been raised elsewhere nor used in any case in this series, because it is my observation that no matter what the degree of the cleft may be, the occlusion of the upper and lower jaw is normal. Any surgical attempt to narrow the cleft is impossible. In all but 6

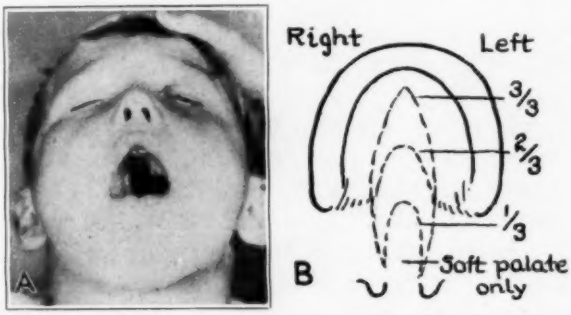


Fig. 6.—Group II, postalveolar cleft. Illustration of this type of the defect is limited to *A*, as it is difficult to photograph the various degrees which are indicated on the diagram.

cases the presence of a cleft hard palate has evolved a situation which raises the question of the sequence of repair of the hard and of the soft palate.

The II–3/3 Palate: The repair of a II–3/3 palate is one of the greatest problems in this field. Fortunately, in my series there were only 11 cases with a defect of this degree. The septum and vomer are exposed their whole length. The condition looks like a double cleft palate, but it is simply a medial cleft which has extended to the anterior palatine foramen, as far as the cleft may go without involving the alveolar process, in which case it would be recorded under Group III.

Operation on such a combination has never been attempted in this series before the child is 2 years old. In several cases the operation has been postponed until the child is 3 or 4 years of age. The tissues grow with the body, and during this period there is some normal adjustment and development of resistance to handling.

At this point it seems fitting to discuss the problem of the sequence of operation on the hard and soft palates with the understanding that the statements apply not only to the II–3/3 palate but to the other combinations as well, that is, the palates in Groups II and III.

The sequence of operation on the hard and soft palates may be solved by several plans.

1. An attempt may be made to suture both the hard and the soft palate at one sitting.

2. The hard palate may be sutured, and the soft palate left for later repair.

3. The soft palate may be sutured, and the hard palate left for later repair.

4. The soft palate may be sewn and the hard palate raised and packed for several days, when the packing is removed and a delayed suture of the mucoperiosteal flaps is made.

Plan 1 has not yielded a primary result in the cases of the II–3/3 palate. In 1 case the right mucoperiosteal flap sloughed out, and although this healed so that the closest inspection was required to see the loss, this plan appears to me to exceed the possibilities of the tissues and should be put aside in favor of other steps of sequence.

Plan 2 is satisfactory because the hard palate will always heal, even in the presence of infection. If infection should occur, the fact that the soft palate is unrepaired affords wide avenues of drainage. This plan has not been used for postalveolar process clefts, although it has become popular with me in the repair of the palate in the Group III case, for it appears to offer the best chance of solving that problem.

In plan 3 the soft palate is sutured, and the hard palate is left for later repair. The effect of such a procedure is the same as that obtained with plan 1 when the suture line of the hard palate fails to hold. In the repair of the soft palate it is always necessary to mobilize the hard palate, the handling of which results in an inflammation which is residual over long periods, and unless the secondary suture is undertaken within ten days or two weeks, it seems wise to postpone it for six months or more. The high percentage of success in secondary repair of the hard palate may support this plan, but it has purposely not been followed in any case in this group.

Plan 4 has been done several times, and the ratio of success to failure of 2:1 (see part III) is illustrated by my experience in 3 patients who were under my care at the same time. In 2 cases there was apparently a perfect result, while in the other the child had a high temperature and was prostrated, so that any immediate secondary repair was precluded and the procedure resolved itself into plan 3. An objection to this plan is that a second anesthetic given within a period of from seven to ten days following a rather elaborate procedure carries a risk which must be carefully considered in the individual case.

As previously stated, the Group II–3/3 combination presents one of the greatest problems in this field of surgery, and whenever a primary result is attained I consider it a great victory.

In my experience the best chance of success is with plan 4.

The II-2/3 Palate: This defect is shown in figure 6, and it occurred 22 times in my series.

In this type of defect there is a good chance of obtaining a primary result with the straight Langenbeck-Warren operation of median suture, viz., plan 1. There is an occasional case which apparently merges into the combination just described, and plan 4 has been tried.

The 2–1/3 Palate: For this combination, of course, there is only one method of repair, plan 1, because it is seldom that more than two stitches, usually superficial, are required in the hard palate. But I have found that these may fail as well as a whole suture line.

The earliest age at which operation was performed in the series was 6 months, but the baby was large and strong, and the result was perfect. I still feel, however, that at such an age the risk is too great, and the operation should be postponed to the second year or later.

Soft Palate Only: There were only 6 cases in which the soft palate alone was involved. It is interesting to me to find that of the 7 cases of operative failure in cleft of the soft palate, there were 1 secondary and 2 primary failures in this simple form (part III).

An interesting condition appears in the soft palate which is not evident until the child begins to talk. A transparent median line is not found until the child develops a nasal tone in speech. The mucous membrane has healed, but the muscles are apart. I believe that a child with this defect is entitled to a formal repair in order to effect contact of the muscle bodies.

In Group II there were 56 cases in which operation was performed. This number in no way represents the real relative incidence because these patients are under observation and preparation for operation over long periods. The average age at which operation was performed varied from 14 months to 2 years.

Group III. Alveolar Process Cleft (figs. 7 and 8).—The value of the classification and plan of record is most evident in this group. In Groups I and II the combination and degree of the clefts run rather closely to form because the alveolar process is closed. When the process is cleft, as in Group III, there are so many possible combinations and degrees of failure in embryonal growth that the usual terms of description appear most inadequate.

The chart allows the description of each cleft separately, viz., the lip, alveolar process, hard palate and soft palate. Several combinations may be thus accurately described—cases which it is not possible to record clearly in any other way.

The incidence of the various combinations in this group is as follows (fig. 7):

Defect	Cases	F.	M.
III L. C.	110	33	77
III R. C.	55	17	38
III. B.	51	17	34
Total	216	67	149

216 of 350 = 61.7 per cent.

Fig. 7.—Group III, alveolar cleft: *A*, right complete; *B*, left complete; *C*, bilateral.

Fig. 8.—Group III, alveolar cleft with normal palate: *A*, right complete; *B*, left complete; *C*, bilateral.

The incidence of 61.7 per cent is the largest of any combination of the clefts. All of the clefts are present. The cases vary greatly in degree, not because of the lip or palate cleft, but on account of the process cleft. The literature revolves about this group.

The statistics on these combinations with a normal palate follow (fig. 8):

Defect	Cases	F.	M.
III L. C.	24	7	17
III R. C.	11	7	4
III B.	7	2	5
Total	42	16	26

42 of 350 = 12 per cent.
258 of 350 = 73.7 per cent.

The incidence in the subdivision of Group III appears between that of Group I and Group II. The statistics of 12 per cent is close to similar reports of the literature.

About three fourths of all cases are recorded in the third group. The operator's problems in repair of the lip and of the hard and the soft palate in this group are generally the same as in Groups I and II. But a problem appears which has so deeply impressed me that I believe it should be identified as the most important in the whole field of surgery—the cleft in the alveolar process. What shall be done for it and when? Various avenues of study indicate, if they do not prove, that the cleft in the process is a separate cleft from the others and is particularly important because it involves the most resistant of the tissues of the body—bone. The time of operation is therefore more important than with other clefts which invade soft tissue only. Soft tissue may be mobilized at any time of life, but with the bone cleft there is only one time when this cleft may be closed, and that is as early as is compatible with the condition of the child, while the bones are soft and pliable. If the baby is allowed to grow to the age of 3 months and beyond, the bones become set and fixed, and it is increasingly difficult to effect contact of the margins of the cleft. The various plans of repair used in this series, the results and the discussion of the relative value of direct force and indirect force will be found in part III.

Whatever the plan used, I repeat that the ease of accomplishment and the effect depend entirely on the softness of the bones and the width of the cleft. The cleft of the alveolar process is the first one to be considered.

The cleft of the lip is second in importance to that of the alveolar process in the consideration of the age for operation and the sequence of the steps in this group. In Group III the lip has been repaired as early as possible, not only because of the appearance and function of the lip itself, but particularly because of its effect in closing the cleft of the alveolar process underneath. Although the forms may be the same as in Group I, the lip in Group III is associated with a bone cleft of the alveolar process. Most lips are repaired before the child is 3 months of age.

The clefts of the hard and soft palates have never been repaired before the fourteenth month, as stated in the section on Group II. At this time the child is observed and operated on if the cleft at the junction of the hard and soft palate measures no more than 10 mm. Often the operation is postponed until the seventeenth month, and more recently until the child is 2 or more years of age.

Observation of the results of repair of the hard and soft palates has brought up another question, viz., the selection of the time of operation. The latitude (45 degrees) in which St. Paul is located exhibits wide

ranges of weather which influence the patient's reaction to these changes. Since the child must be hospitalized and often comes from long distances, this phase of the subject should be carefully considered. In repair of the clefts of the alveolar process and of the lips the question of selection of the time for operation is minimized because the cleft of the alveolar process should be molded and the lip repaired early. The question, however, is most important in repair of the hard and the soft palate as infections may lead to failure. These operations are often postponed in the expectation of equable weather.

The subdivision of Group III (fig. 8) that is most interesting to me is the combination of a cleft of the lip and of the alveolar process but normal hard and soft palates. These cases support the statement that the alveolar process cleft is not a part of the palate, but is formed in relation to the lip.

This combination occurred in 42 cases. Figure 8 *A* shows this condition excellently. In figure 8 *B* it is not so evident. In figure 8 *C* is illustrated a problem which is almost as great as that presented by the II–3/3 palate. In this case the large premaxilla apparently has no place between the two lateral divisions which appear close together.

The law of early repair of the alveolar process also holds in this combination. The premaxilla must be pushed down as early as possible. The question of the use of direct force through wires has never been raised in this combination. There is a tendency to delay replacement of the premaxilla because the palate is normal, and apparently there is nothing to repair but the lip. Yet in this combination there are more unsatisfactory nostrils than in any other, owing to the fact that an attempt to close the alveolar process cleft is postponed until the lip is repaired.

The photographs of the six cases in Group III (figs. 7 and 8) merely represent typical cases. Added to these are many of different degrees. An exact record of the original condition is necessary to appraise the results of late repair properly and to evaluate the surgical principles of repair. The classification and plan of record appear to meet the requirements.

By reason of the great variety of combinations and degrees, rules of procedure can be only generalized as follows:

1. Repair of the alveolar process cleft should be done first as early as is compatible with the condition of the child.

2. Repair of the lip is left to the judgment of the operator. The age for operation depends on the degree of the cleft of the alveolar process.

3. Repair of the hard and the soft palate in Groups II and III should be postponed to the second year or later, with particular attention to the

season selected for operation. The sequence of operation in the wide clefts should be considered. I have a preference for suture of the palate first and later repair of the soft palate.

III. OPERATIVE RESULTS AND TECHNIC USED

The 350 children were subjected to 567 operations; that is, some procedure or combination of procedures was performed which required an anesthetic. The disparity between the total number of cases (350) and of operations (567) is explained in part by the fact that during a long period of trial and error, different sequences of steps were used; the hard palate was repaired and the soft palate left, or the steps were reversed; or the alveolar process was wired and the lip repaired at a second sitting, etc.

The mortality has been 1.4 per cent of the total number of patients (350)—less than 1 per cent of operations (567). Two patients died of pneumonia: One, a child in whom the whole palate was repaired, died on the twenty-first day, although the stitches held; the other child died on the sixth day following repair of the lip. One patient, 6 weeks old, died of erysipelas, which developed in an abrasion of the left cheek, and although the stitches held in a bilateral cleft of the lip, death occurred on the tenth day. A patient subjected to repair of a unilateral cleft died the afternoon of the operation from suffocation due to inspired vomitus, as proved by autopsy. The fifth patient died on the operating table from an undetermined cause other than shock.

When one considers that the babies and children in this series were operated on at several different hospitals, with a changing group of anesthetists, and that as a class the patients are delicate, the record appears favorable. It is due in part to the fact that no operation was undertaken without the permission of a pediatrician, and again to the rule that when bleeding occurs during one stage of the operation, it shall be completely controlled before another stage is undertaken. So often postoperative concern is due not to the length of operative time or to the quantity of anesthetic, but to the loss of blood.

In the study of operative results the plan of the classification has been followed wherein the whole palate is resolved into its component clefts. The lip, alveolar process and hard and soft palates have been studied separately to determine, if possible, wherein lies the greatest chance of failure or of success. Most of the children have received my personal attention, except those at University Hospital, where I have had the assistance of my associates, Dr. Carl Waldron, Dr. W. T. Peyton, Dr. Logan Leven and others who from time to time have been interested. But since in all cases I have assumed some measure of responsibility, it seems fair to include them.

Cleft Lip.—At first I intended to separate the incomplete and complete forms of cleft lip, but so many of the so-called incomplete forms, whether in Group I or III, were found to be complete as regards muscle contact and to present the same problems of repair that they are discussed together here irrespective of the degree of the cleft. In the repair of this defect I have used my interpretation of the Mirault operation, the Rose operation, the Nelaton flaps, the modified Hagedorn and Thompson calipers, etc., but the large majority of clefts have been repaired on a principle suggested some years ago and called "a muscle theory repair of the lip." The theory was based on the observation that the general scheme of formation of all lips was the same in all persons, but with infinite variety of detail in the disposition, control

Fig. 9.—Photograph illustrating the muscle theory repair of the lip. The same picture may be obtained in the infant by electrical stimulation, not only before operation, but after suture.

and development of the tissues. The theory is simply illustrated in figure 9, the photograph of a boy of 8 years who grew to this age with his lip out of contact. It is to be observed that the active tissues of the lip develop along with the body, and that physiologic action is under the control of the person at all times and under all circumstances (fig. 9 *A*). The most direct plan for repair appears to be to suture the lip on lines of denudation determined by the active elements of the lip in the hope that if the parts are united at the peak of their physiologic action such effort will yield the best chance of anatomic replacement normal for that child. In the infant, when stimulated by the battery before operation, the same picture as illustrated in figure 9 is obtained. On every possible occasion I have stated and reiterated that this theory presented no new operation, but was simply an effort to determine a common principle of repair which would fit anatomic and physiologic require-

ments, no matter what the combination and degree of the cleft in the lip might be. The anatomic basis has been challenged because it may be safely said that no two lips are exactly alike. I have tried to dissect the orbicularis oris in the infant cadaver, and it cannot be done. Whatever may be the anatomic picture in a given case, there is always present the physiologic action which produces the pucker of the lips. The symmetrical pucker depends on the normal direction of the muscle bundles and, if the effort is made to maintain these relations without distortion, the infant presumably has a better chance to develop its proper facial expression. The theory appears to have a logical conclusion, but, of course, can be supported only by clinical evidence.

The statistics on the lip are as follows:

No. of cases on which operation was done	Left	160	296, or 84.5% of total (350)
	Right	77	
	Bilateral	59	

No. of failures	Complete	3	47, or 15.9% of 296 cases
	Partial	4	7
	Flat and flaring nostril		28
	Narrow nostril		4
	Kinky nostril		4
	Vermilion border notch		4

In 47 cases, or 17 per cent, I made a note to show that I was dissatisfied with the result. I feel sure that this percentage would be largely increased by the legitimate criticism of colleagues, and voluntarily increased in the late appraisal of the cases.

There was complete failure in 3 cases: A bilateral cleft lip separated with loss of tissues in the prolabium—a horrible deformity, one of the great tragedies in this field. One unilateral cleft lip separated its whole length after repair without apparent infection. This is the only case in which a secondary repair was immediately attempted with a second failure of union. Figure 10 shows the result of a delayed third effort. This case supports my general idea that should failure occur, follow-up repair should be postponed until inflammatory reactions have subsided. One side of a bilateral cleft failed to hold, and follow-up closure was done (fig. 11). I do not find such experiences illustrated in the literature, and I thought that it might be interesting to show the usual picture. In the bilateral case the principal point of criticism is that the muscle elements are probably out of contact. If this is so, the lip will not grow along with the body and the chances are that a flat, immobile lip will result.

My charts contain notes on partial failures, the most frequent of which is the resulting flat and flaring nostril. The deformity of the nose is so apparent that I find myself often evaluating the result of

Fig. 10.—The photograph of the result of a third operation in the case in which the primary and secondary repair failed.

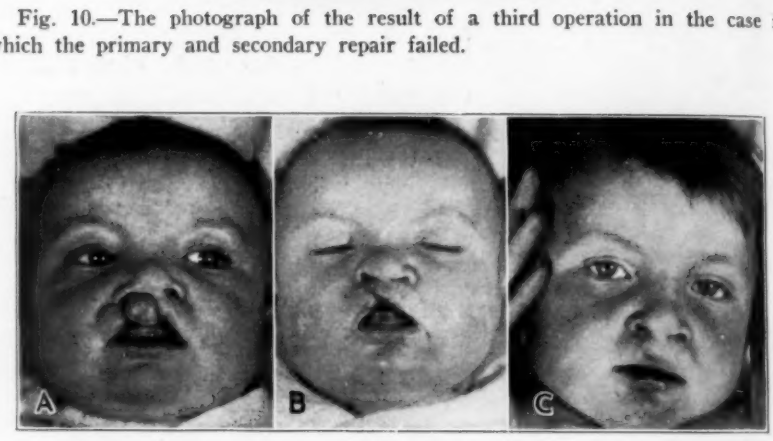


Fig. 11.—The original condition in this case is used to illustrate a Group III bilateral alveolar process cleft (fig. 7 *C*). Both sides of the double cleft were repaired at one sitting. The right suture line failed to hold (*A*) and was repaired in six months (*B*). The condition when the boy returned for repair of the palate is shown in *C*.

Fig. 12.—Flat and flaring nostrils following repair of a right and left complete cleft lip.

repair of a cleft lip by the condition of the nostrils. Reposition of the ala in the unilateral cleft to compare favorably with the normal has been the *bête noir* all through this work. The cause of this frequent postoperative deformity is suggested by the following study. Figure 12, which illustrates the situation, shows a right and left unilateral cleft determined by measurement with calipers and by electrical stimulation. The measurement indicates that the flat nostril is due to the fact that the floor of the reconstructed nostril is twice as wide as the normal, as shown by the dots. Stimulation reveals that there is a V-shaped piece of tissue in between the upper bundles of the active tissue which are out of contact at this point. The body of the lip, the line of the vermilion border, the eversion of the mucous membrane and the mobility of the whole structure have been obtained not as a result of any personal

Fig. 13.—*A* is a tracing made from the diagram in the work on embryology by Fischel of Vienna. *B* shows the attempt to follow the marking of the tracing in a clinical case. *F N P* indicates frontonasal process; *L N P*, lateral nasal process; *M P*, maxillary process.

opinion of mine as to how the repair should be made, but simply on lines of denudation determined by the active elements. Thus the main lead to proper repair of the body is offered by the arrangement of tissues peculiar to the case itself. However, the nostril may or may not be in proper form, and if it is not a striking deformity results. An explanation of the double nostril must be found. Fischel of Vienna, in his text on embryology, states clearly that the complete cleft of the lip is a combination of two embryonal clefts (fig. 13 *A*). The cleft in the body of the lip involves the active elements. Its presence is due to a failure of contact of the lateral maxillary process and the infranasal process of the median embryonal division. An extension of the cleft beyond the structure of the lip does not extend into the nose but runs outside of the ala through the cheek and may reach the eye to form a coloboma. The case of multiple clefts of the face (fig. 7) indicates

the direction and possible extent of this cleft. The cleft in the floor of the nostril is a different cleft formed entirely in the median embryonal division. Its presence is due to a failure of the lateral nasal process to establish contact with the globular process. In order to follow clinically the embryonal diagram (fig. 13 *A*), markings were made on an incomplete harelip (fig. 13 *B*) to indicate that the tissue in the angle between the two clefts is probably an extension of the lateral nasal process. I have cut this reflex tissue away from the columella (fig. 14), denuded it and sewed it back on the maxillary tissues. The result was a perfect picture of a complete harelip. When the maxillary process was denuded, the muscle elements, as shown by the stimulation with the battery, were superficial and reached squarely to the margin of the cleft. When the band was sutured, the muscle ends were deeply placed. It appears to me that in both unilateral and bilateral harelips there is a reflection of the

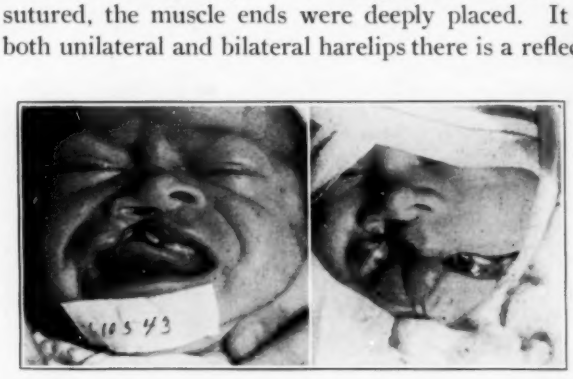


Fig. 14.—The experimental operation described in the text undertaken to determine the embryonal origin of the reflection of the incomplete cleft lip and the position of the reflection in the complete cleft lip.

lateral nasal process onto the body of the lip. This growth is epithelial tissue only and covers the upper bundles of the active tissue of the maxillary division. The explanation of the flat and flaring nostril can now be fairly made; this tissue has been brought into the body of the lip, whereas in the complete cleft lip it should be lifted in order to denude the upper bundles of muscle for exact suture to the bundles of the other side of the cleft.

In figure 15 *A*, the diagrammatic denudations for the body of the lip are correct, but at the nostril the tissue in the grasp of the mattress stitch, without particular attention to its position, may be brought into the body of the lip instead of being turned into the nostril, as in figure 15 *B* and *C*.

The steps of the operation for unilateral cleft lip as performed are as follows:

The muscles are stimulated by the battery, and the lowest and highest points of motion are marked by ink dots. On the medial side of the cleft, two marks only are required, one at the vermilion border and one at the base of the columella,

so that denudation for exposure of the muscle elements is always in a straight line. On the lateral side of the cleft, the muscle elements are apparently bunched. Three points are determined: one at the base of the ala, one on the vermilion border and a variable point on the margin of the cleft. The denudation of the short side is always staggered. The distance between the ink mark at the base of the ala and the point on the margin of the cleft is measured by the caliper, one point of which is placed in the upper ink dot on the medial side and the other point is swung into the nostril along the epithelial reflection at the base of the columella.

The denudation of the medial side is made by connecting the upper and lower ink dots on the body of the lip by an incision at the margin of the skin and the careful dissection and removal of the mucous membrane. The skin and mucous membrane are undercut in order to make the body of the lip a separate entity. The ink dot in the nostril and the upper ink dot on the lip are connected by an incision. The epithelial reflection in the nostril is thus raised in the form of a flap to become the inner half of the floor to the nostril. On the lateral side of the cleft, the ink dot at the base of the ala is connected by an incision through the skin only, with the ink dot on the margin of the cleft. This is dissected to make a flap, which becomes the outer half of the floor of the nostril. The raising of this

Fig. 15.—*A*, a copy of the original drawing demonstrating the repair according to the muscle theory. *B* and *C* illustrate the incision for the flap and the points of suture. It is difficult to draw this important step of lifting the flap from the muscles. The incision *1-2* connects the ink mark at the base of the ala and the ink mark on the cleft margin. The flap raised is triangular in shape with the point of the triangle at *1*. This step permits exact suture of the muscles at *2* and *2'*. The tip of the flap at *1* is sutured to the epithelial flap in the nostril at *1'*.

flap bares the upper bundles of muscle elements on the short side. The ink mark on the margin of the cleft is connected with that on the vermilion border, and the mucous membrane is dissected as on the medial side. On the body of the lip the effort is made to obtain the picture shown in figure 15 *A;* on the nostril, the picture shown in figure 15 *B*. The stitches used are the same as shown later in figure 30, but they are placed on the mucous membrane side, except at the vermilion border, where it is important to make more exact approximation of the muscle elements on account of the vermilion border of the lip and the eversion of the mucous membrane. In this lower stitch, the simple end-on stitch is used. I have always had the idea that the top stitch of the muscle *2-2'* (fig. 15 *B* and *C*) would determine the rotation and position of the ala. This idea I have found correct. The difficulty has been to find a way to make the approximation exact.

Since these steps are more fully developed, there has been a definite improvement in the results with some excellent replacements, of which figures 16 and 17 are examples.

Fig. 16.—*A*, Group III unilateral cleft, right complete, showing the original condition when the mouth is stretched. *B*, the repaired lip at rest.

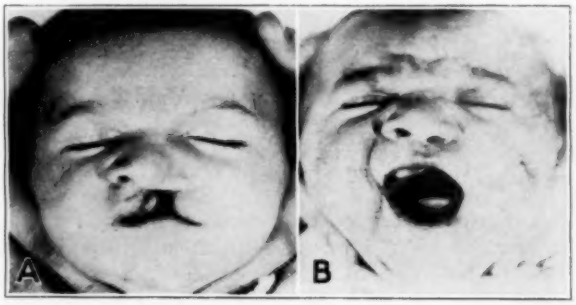


Fig. 17.—*A*, Group III unilateral cleft, left complete, with the original condition at rest. *B*, the repaired lip when stretched.

Fig. 18.—A case of double cleft lip shown to support the statement in the text that the failure of the columella to grow and the nose to project is due to the wide separation of the ala.

In the cases of the kinky nostril many things have been tried, but the rotation of the ala appears to correct this deformity as well as any method.

Bilateral Cleft Lip.—In double harelip, the nostrils may be made to look alike; at least there is seldom the gross deformity evident in the comparison of a poorly constructed and a normal nostril.

The trouble in this form of lip is in the tip of the nose and the growth of the columella. Figure 18 is shown as a probable explanation of this condition. The alae are twice as far apart as normal, and the effect is as though a rubber band had been drawn taut over the tip of the nose so that this part could grow only by separation of the cartilages. The failure of the nose to project properly has led to many suggestions for repair, the most interesting of which brings up a legitimate question as to whether the prolabium of the lip belongs to the

Fig. 19.—*A*, the combination of cleft lip in which one side is complete and the other incomplete. The follow-up picture (*B*) shows that the prolabium will develop if properly placed. Note the double nostril on the left side.

columella, to be used to add to its length, or whether it belongs to the body of the lip.

From the embryology it appears that the infranasal process of the median division extends downward to be incorporated into the vermilion border of the lip and joins the maxillary divisions on either side. Clinically, this fact is supported from several angles, but particularly in the case (fig. 19) in which there is a complete cleft on one side and an incomplete cleft on the other, with the prolabium presenting in various states of development. The temptation to do something to supplement the tissues of the prolabium is great, but to do so would bring tissue away from the normal area—if the statement that this structure is a part of the lip is correct.

The case shown in figure 19 was selected for two reasons: First, the suture lines are more evident than is to be desired, but the picture shows

plainly the plan of repair with normal growth of the prolabium if given a chance, and second, the double width nostril is present. The latter condition may not be a gross deformity, but in this case the right nostril has not been properly reconstructed.

In complete double harelip there is now sufficient evidence to state that there is no muscle in the prolabium. Stimulation with the battery fails to obtain action, and Mullen, in a more recent paper on the comparative anatomy of this area, brings definite support to this statement. The muscle elements formed in the maxillary divisions migrate to interdigitate between the skin and the mucous membrane of the prolabium to form a normal lip.

Thus, in all cases except a trial case here and there, the effort has been to bring the prolabium into the body of the lip and to make as direct contact as possible of the muscle elements of the lateral divisions.

Double harelip has been repaired in three ways.

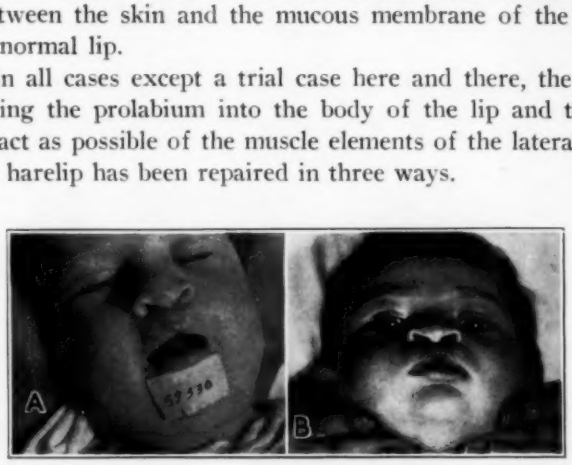


Fig. 20.—*A*, the result of a modified Hagedorn operation. *B*, the result following an attempt to bring into contact the musculature of the right and left maxillary divisions between the skin and the mucous membrane of the prolabium.

Figure 20 *A* shows what is interpreted to be a modified Hagedorn operation, differing only in degree from Hagedorn's original illustrations. The mucous membrane of the prolabium has been sacrificed, and the maxillary divisions are brought in direct contact below it. Clinically, these tissues may grow well but there is a risk of a tight lip at the vermilion border and a bunching effect of the prolabium because it has little chance to grow downward.

Figure 20 *B* shows a case in which repair was done by denuding the maxillary process along lines determined by the battery. The sides of the prolabium were denuded between points measured by the calipers to equal the sides, the prolabium was tunneled and then effort made to directly appose the muscle elements through the tunnel.

Figure 21 shows the plan by which one side is repaired at one sitting and the other side is repaired after a six weeks' or two months' interval. For a long time I deprecated the last method because of its effect on the

premaxilla of the alveolar process. Great pains have been taken to replace this structure, and when the lip is repaired it is immediately displaced. But on the second repair, the premaxilla evidently assumes its former position. The photograph of this patient shows clearly the effect of the lip on the alveolar process cleft. The plan of two operations has recently become more popular with me. The attempt to sew both clefts and replace the ala approaches at times a formidable procedure, and it is a great relief to repair one side at a time. It has been found possible to bring the active elements of the sides to the middle of the prolabium; when this is done the second time it brings these elements almost if not exactly in positive contact. At any rate, the end-results yield motion in the prolabium when stimulated by the battery.

However, the repair illustrated in figure 20 *B* is more direct and follows the muscle theory more closely, if it can be technically accomplished. In all cases the flaps have been turned into the nostril.

The solution of the problem of repair of a cleft lip is so important for the future comfort and social happiness of the child and it is therefore such an enormous responsibility for the surgeon that these suggestions and reports must be carefully considered before attempts are made to follow the principle.

The arguments for symmetrical contact of the muscle elements appear so logical and so well supported clinically that whatever the technic may be, the steps will be analyzed as to their effect on the muscle elements.

Embryologic and clinical study of the lip indicates two separate principles: muscle repair for the body of the lip; plastic repair of the nostril.

Alveolar Process Cleft.—The statistics on the alveolar process cleft are as follows:

Incidence of cleft ranging from notch to wide clefts	258, or 75.7% of 350
Wired	71, or 27.5% of 258
Vomer cut { front 3 / back 8 }	11
Undercorrected / Overcorrected	?

In three fourths of all cases the question of the procedure for the closure of this cleft arises. In all cases I have followed the broad general principle that the cleft in the process is a bone problem. To mobilize bone, force is required, either direct or indirect, or both. The relative merits of each have been discussed in the literature with great diversity of opinion, which ranges from the advocating of direct force through the medium of wires and plates to the view that one should rely on the indirect force of the musculature of the face and specifically

of the lip. In this series both principles have been used and in several combinations, depending on the age of the infant and the degree of the cleft.

The plans may be noted as follows:

1. Molding of alveolar process by thumb pressure; repair of lip at same sitting.
2. Molding of alveolar process; adhesive strap to face; repair of lip delayed.
3. Molding of alveolar process; insertion of holding wire; repair of lip delayed.
4. Molding of alveolar process; insertion of holding wire; repair of lip at same sitting.

1. Molding of Alveolar Process by Thumb Pressure; Repair of Lip at Same Sitting: To report statistically on the degree of the defect would require a description of each case because no two cases are exactly alike, but a broad statement may be made that the defects in a large number of unilateral cases run from 6 to 12 mm. The width of the unilateral cleft is due to the pivotal displacement of the median frontal nasal process, which has united with one or the other maxillary division which is carried along in the pivot. In the bilateral case the measurements have an enormous range with inequality of the sides due to the projectional and rotational displacement of the premaxilla, which is out of contact with both maxillary divisions.

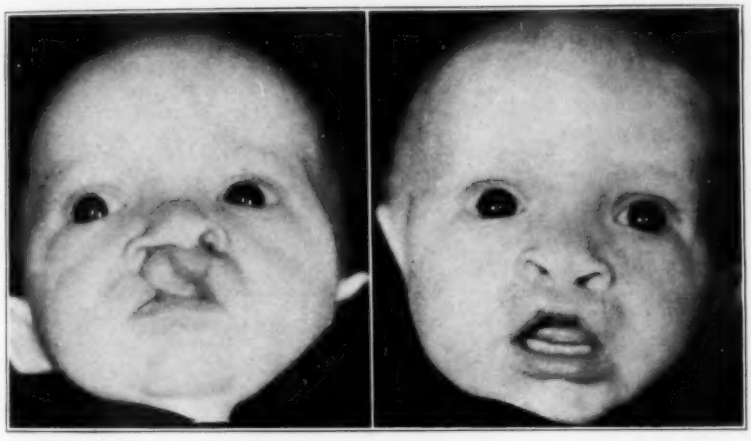
All through the series, whether unilateral or bilateral, a great effort was made to follow plan 1 as the simplest and most direct way, accompanied by a minimum amount of traumatism and reaction. For the notch, in the 2, 4, 6 and possibly 8 and 10 mm. clefts of the alveolar process, there is no debate as to the propriety of this procedure, and it is quite the rule that in clefts of these degrees the cleft is closed by the time the stitches are removed from the lip. The plan has been tried in the wider clefts, 8, 10, 12 and 14 mm., with varying results. If the bones are soft and pliable and the degree of the cleft is easily changed by pressure with the thumb to 4 mm., the cleft in the alveolar process may close early, but more often the change is gradual. On the other hand, the plan has proved incomplete in the wide clefts or in the clefts of the older babies. There are cases in which the alveolar process is not closed over a period of four years.

In the clefts measuring 8 mm. and over, some supplementary step seems to be indicated.

2. Molding of the Alveolar Process; Adhesive Strap to the Face; Repair of Lip Delayed: This plan is as old as the literature on the subject, but has been lost sight of with the development of more elaborate procedures. More recently it has again been used as a preliminary measure to the repair of the lip—a preparation of the bones in order to minimize the loosening of the cheeks which in the wide clefts is necessary to lessen tension caused by the stitch.

There is never an apparent reaction to the procedure; it can be used early and can be repeated often without an anesthetic, in the office or at home. Whenever it is used, constant attention and observation are necessary, because one may be surprised to find that with this simple step overcorrection or overlapping of the margins of the cleft may occur in some cases. However, the tendency is for the bones to spring back into the original condition. The straps must be repeatedly tightened and continually applied up to the time of the operation on the lip, or the purpose will be defeated.

An increasing number of infants have been satisfactorily treated in this manner—infants who in the past would have been subjected to the more formidable operations to be described.



A B

Fig. 21.—Double cleft lip repaired at two sittings, six weeks or two months apart: *A*, repair of the left cleft; *B*, repair of the right cleft and final result. The original of this case is shown in figure 24 *A*.

3. Molding of the Alveolar Process; Insertion of Holding Wire; Repair of Lip Delayed: As a student of the wonderful literature on this subject, I was deeply impressed by the teachings of the late Dr. Brophy. Based on experience in thousands of cases, ingenious plans were promulgated for the use of direct force applied to the upper jaw through the medium of wires and plates. The steps were based on the concept of a whole or a complete cleft palate and the theory that the width of the cleft was due to the lateral separation of the bones. (This is a purely personal interpretation of his principles.) In several cases not included in this series, these plans were used in operating, but were not used in subsequent cases for several reasons:

1. Individual technical inability to apply the wires and plates without seemingly undue traumatism.

2. Observation and study which led to the belief that the width of the clefts was due to the obliquity of the palatine processes in the hard palate plus the odd and bizarre positions of the premaxilla.

3. Occurrence of a cleft palate which was always median in the hard palate and lateral in the alveolar process, but never a straight line complete cleft palate.

4. Overcorrection of the maxillary process and malocclusion with the mandible.

5. The fact that the bone problem lay in the process and not in the hard palate.

In spite of these ideas, I accepted the principle of direct force in any form because the process was normally formed in bone and sug-

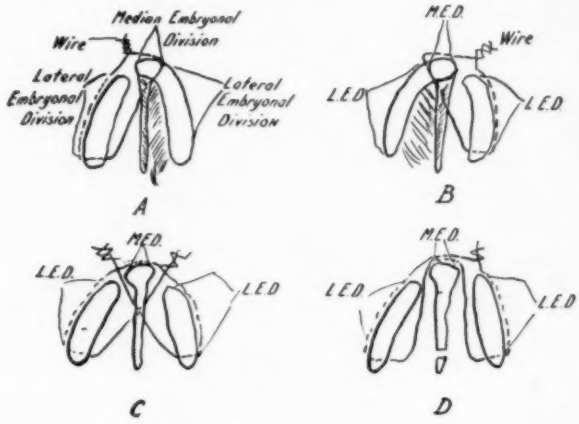


Fig. 22.—Tracings of the various plans offered for the application of direct force to the upper jaw by the use of holding wires. *A* shows the technic in the repair of the right cleft; *B*, of the left cleft; *C*, the combined technic applied to the bilateral cleft, and *D*, circumferential wiring.

gested the use of wires inserted along lines developed for the study of the embryology of this part of the body, illustrated in figures 22 and 23, i. e., direct force applied to the median division only.

The survey reveals that wires were applied in 71 of 258 cases. This was somewhat of a surprise. It appears that I was more interested in establishing the principle than I was in its use.

During a period of trial and error, there were 2 cases in which the wires were applied on an 8 mm. cleft, but most of them were used on the wider clefts, which at the time of the operation, on account of width or rigidity of the bones, could not be brought down through pressure to a point where a lip could safely be sutured with the expectation that it would close the cleft of the alveolar process.

It has never been possible to close the cleft of the alveolar process entirely by such measures (fig. 23 *A*). To attempt to do so requires undue force which may affect other structures than the premaxilla. When the repair of the lip is delayed, the wires should remain in place until the lip is sutured. In the unilateral clefts (figs. 7 *A* and *B*) the results were variable and often not permanent. I have watched these babies over a period of from four to six weeks and have then removed the wires; in two or three days the bones spring back into the original condition just as when plan 2 is used, so that nothing is really accomplished until the lip is repaired.

In cases of bilateral clefts (fig. 7 *C*) the maxillary divisions appear to me to be always in position with normal occlusion with the mandible, so that the marked deformity is in the median division with the projec-

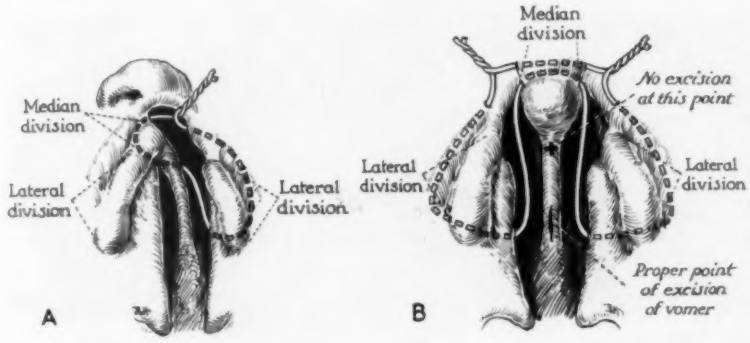


Fig. 23.—*A*, a formal drawing of the plan for wiring the right or the left unilateral cleft. *B*, the plan for circumferential wiring of the jaw for the bilateral cleft. The change from the original drawing is that a short wire is used in front in order to get a right and left twist instead of one. The rotation of the premaxilla is more easily controlled.

tion and rotation of the premaxilla. Something must be done to replace this structure in contact with the two sides. In this combination plan 3 has been more satisfactory than in any other case, and apparently is the only way in which the extreme degrees have been successfully treated.

In some cases the projection is great on account of an apparent overgrowth of the septum and vomer, so that it is necessary to section, fracture or remove part of this tissue. Incision or excision in front (fig. 23 *B*) has been long discontinued, on account of the possibility that growth of the premaxilla may be inhibited. Instead, the base of the vomer is attacked; the wires are placed as in figure 23 *B* and are left until the injury is apparently healed, when they are removed and the lip is sutured. The immediate effect of such a procedure is shown in figure 24 *B*.

4. Molding of the Alveolar Process; Insertion of Holding Wire; Repair of Lip at Same Sitting: This procedure has never been used on the bilateral cleft. The repair of the lip is exacting and time-consuming. When two operations are done at one sitting, the patient may become exhausted. Such a consideration as this, here and elsewhere, is another factor in my low mortality rate. In the cases of unilateral cleft there is the best chance of success. In fact, in some cases the alveolar process is closed so promptly that a question is raised as to the necessity of the application of the wire.

Plan 4 is generally recognized. There is a diversity of opinion as to the materials used—silver wire, silkworm gut or soft material, trocars, large or small, straight needles, etc.—and there are different ideas as to points of insertion.

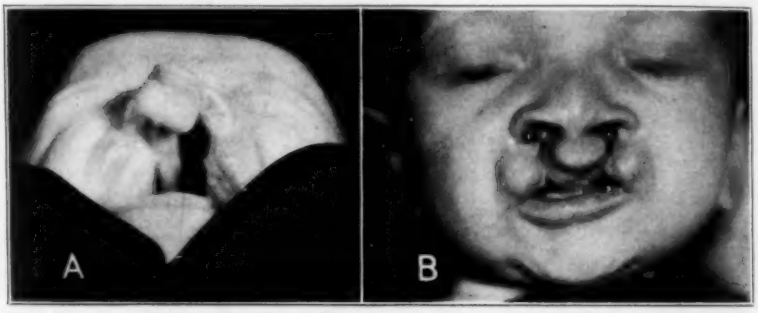


Fig. 24.—Photograph of a successful result in a Group III bilateral cleft in which the premaxilla was subjected to the circumferential wiring by the plan shown in figure 23 *B*. The end-result of the operation on the alveolar process and lip in this case is shown in figure 21.

The theory on which the application of the wire is based in the unilateral cleft is that the maxilla in contact is displaced outward secondary to the pivot of the premaxilla septum and vomer, and that force should be applied to the median division only in order to replace it on the maxilla out of contact. The wire in front is inserted at the point of union of the premaxilla and the maxillary division and is carried far back on the side out of contact. The point of insertion in front is definite; that at the rear is debatable. The possibility that the six year molar, a structure essential to the normal growth of the upper jaw, may be inhibited has been offered in criticism of the insertion posterior to it, and must be considered. Wherever placed, something to hold the bones in position to facilitate the operation on the lip appears necessary.

Overcorrection of the Alveolar Process Cleft: The matter of overcorrection or undercorrection of the process cleft is reported with a

large question mark. Whatever the plan used, the results have ranged from excellent closures and contours to those that are overcorrected. The wire has caused overcorrection of the short side in the unilateral clefts (fig. 25), while in the bilateral clefts there are extraordinary deformities in 2 cases, 1 of which is shown in figure 26. The penalty of direct force is a deformity which may be irreparable; although orthodontic procedures may result in correction to some extent, this is seldom complete.

Experience leads me again to state that the handling of the cleft of the alveolar process is the greatest problem in this field of surgery and that the solution probably lies in reiteration and emphasis of the dictum of early operation in order to apply properly the indirect force of the lip which in my experience is the only force of permanent effect.

Fig. 25.—The cast of an alveolar process and palate following repair which shows the penalty of the use of the wire on a Group III unilateral cleft. The process of the short side has been moved inward, a situation which results in malocclusion with the mandible. The illustration also shows the successful repair of the hard palate done on plans illustrated in figure 27. The apparent depression of the suture line is in reality a projecting ridge.

I consider the action of the lip to be primary. The wires are accessory to the creation of this force and limited in their use to the extreme degrees of the deformity.

Cleft of the Hard Palate.—The statistics on this cleft follow:

Incidence of inclusion of cleft palate requiring one stitch			272, or 77.7% of 350
No. of cases in which operation was done			199, or 73.2% of 272
No. of operations in 199 cases			244
Primary failures	whole suture line	32	65, or 32.7% of 199
	front	8	
	back	25	
Secondary repair			44
Secondary failure			7, or 16% of 44
Mm. used			15
Lateral incision packed			17

In 77.7 per cent of the cases the cleft of the hard palate is present in either Group II or III. The review of treatment of this cleft is made with a sense of bewilderment. So many technical steps have been suggested for its closure and so many things have been done in this series that a statement of their relative value would be most unreliable. All cases have been attacked on the general principle that this cleft was not a bone problem but one in which some form of a muco-periosteal flap was indicated and that no matter what the arrangement of other tissue in a given case was, cleft of the hard palate was median up to the anterior palatine foramen.

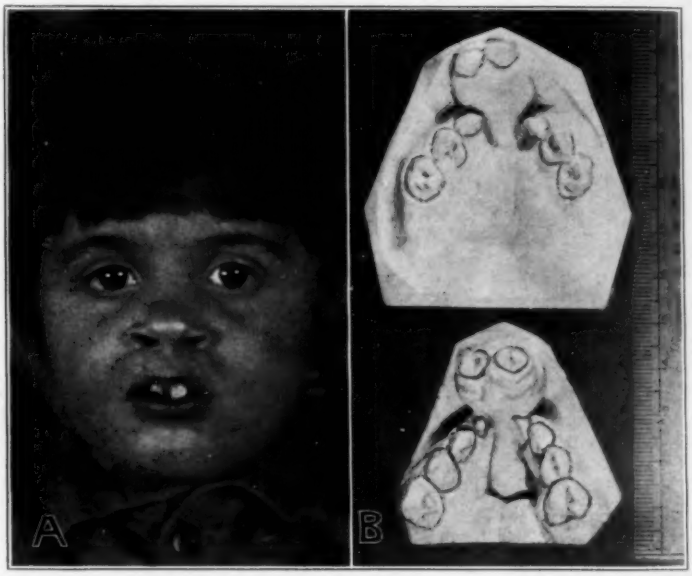


Fig. 26.—A failure of an effort to replace the premaxilla by the plan shown in figure 22 *C*. The upper cast is of the alveolar process and palate of the boy in the photograph. The lower cast is of the alveolar process and palate in another similar case. In both cases the pressure wires used to force the premaxilla into place acted instead on the lateral divisions, which were moved in behind the premaxilla. In the upper cast the hard palate is shown perfectly united. In the lower cast the hard palate is open owing to tubulation and retraction of the muco-periosteal flaps, which were severed from the front attachments.

The question of mobilization of bone appears in the literature, but in no case has lateral pressure by wires or invasion of the palatine plates been done. The latter operation has been done on the cadaver with the observation that the plates must be entered on a line mesial to the hamular process in order to move them toward the midline.

Of all the plans offered, the fundamental technical principle has been the classic Warren-Langenbeck operation of lateral sliding flaps mesially sutured.

The objection to this procedure is the formation of a dead space between the bone and the flap, by which infection is invited. The statistical report of approximately 1 failure out of 3 is valid evidence in support of all those who deprecate this procedure and use various other flap combinations. Infection in the hard palate is the main cause of failure. A high temperature may persist after operation (in one case until the tenth day), with the stitches holding, and not subside until some break occurs in the suture line.

In the palates in Group II, on account of the symmetrical arrangements of the tissue there is not the opportunity or the indication for using many of the accessory steps that are possible in the palates in Group III, which may present great variation in arrangement and contact.

As already stated, all steps have been considered accessory to the lateral sliding flaps. These steps are discussed separately.

Lateral Incisions: In nearly all cases the mucoperiosteal flaps have been raised through a small lateral incision (fig. 27 *A*) made in an imaginary line carried forward from a point outside of the hamular process. The incision is made to the bone in order that the inserted elevator may follow the line of cleavage between it and the flap. In the 1/3 and even 2/3 palates of Group II and in the 6 and 8 mm. hard palate of Group III, the flaps are often raised from the margin of the cleft starting in front where the mucoperiosteum is thick and often built up in rugae, and the danger of a button-hole is minimized.

The incision for elevation of the flaps has been used because in the 10 mm. and larger clefts, something must be done to obtain relaxation on account of stitch tension, particularly in the flat arches. This preliminary step may be extended to any degree, from the soft palate to include the hard palate exclusive of the front attachment, a step which has been done but put aside. In all cases the effort was made to preserve the main stem of the palatine artery. Possibly unwittingly this artery has been injured by elevation of the flaps, but ordinarily I believe it is difficult to sever it without direct effort. In the past two years or so the incisions have been extended on the theory that by doing so the median cleft is divided and transferred equally to the sides, and because relaxation permits of the attempt to replace the mucoperiosteal flaps, by thumb pressure, to establish contact with the bone; the dead space is thereby obliterated or at least lessened.

The objection in the literature to the extended lateral incision is that a fistula may form. In no case under my observation has this

occurred. In fact, the usual experience is that these cuts fill in so promptly that often they are healed by the time the baby leaves the hospital.

Packing the Lateral Incisions: I have found 17 cases in which packs were used. The theory of their use is that by packing the dead space,

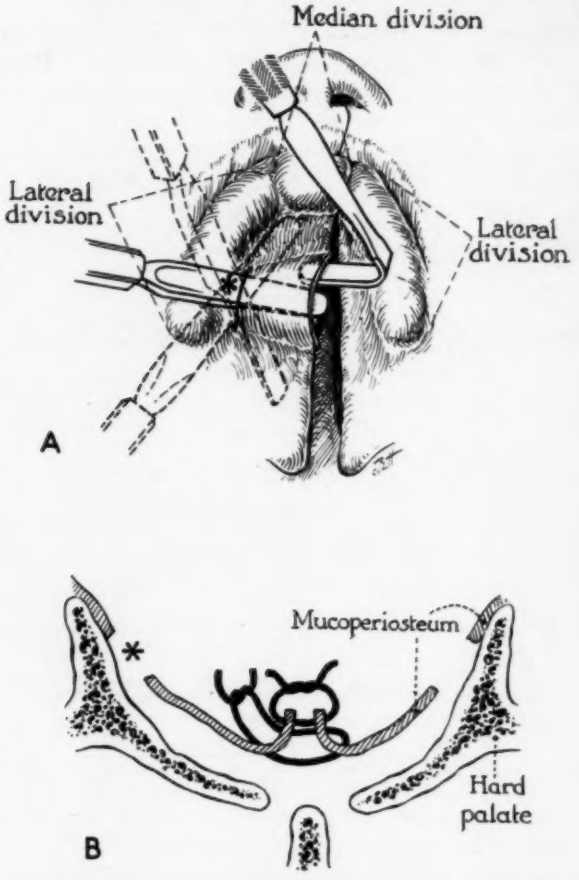


Fig. 27.—*A*, the technic used for repair of the hard palate supplemented by the accessory procedures discussed in the text. *B*, a drawing showing the effort to build the suture line into a raphe.

the upward pull against the stitches and the force of pressure by the tongue are minimized; also, that in some cases, bleeding may appear excessive, and some step appears necessary for safety's sake. In only one case of the whole series did I find a secondary hemorrhage. I found several cases in which a delayed suture of the hard palate had been selected in order to prevent tubulization of the flaps, and packs were

used to hold the flaps in the position until the suture was done. The secondary suture, whether done early or late, is always a difficult procedure in my hands. When done early, the inflammatory reaction present necessitates a most delicate touch, while when it is done late the undercutting of the tube is quite exacting. The packs are gauze strips 1 inch wide. Iodoform, mild silver protein and tincture of benzoin are the chemicals used, with a preference for the last. The objection to the packs is that they soon become foul. I have left them in as long as ten days, but the average time for removal is six days. I believe they are useful in the selected case, but the tendency has been to put them aside in favor of greater relaxation and effort at reposition.

Hamular Process: The arrangement of the tensor palati tissues which loop over the hamular process has led to the suggestion that this structure be fractured to obtain relaxation and facilitate suture and union of the margins of the cleft. For a long time I deprecated this as a destructive and unnecessary procedure. But I have seen it done by expert hands and have done it on the cadaver, during a dissection of these parts. I was much interested to note that the tissues which I interpreted as the tensor palati and the levator palati looked like twin muscles, as though the tensor would assume the function or support the action of the levator. Occasionally in this series the procedure was used, but only in the selected case.

Nasal Mucous Membrane (Vomer): The red tissue over the vomer is wonderfully vital, holds stitches well, can be turned in several ways and appears so resistant to traumatism that apparently in this poor field it might serve as a free graft.

I have turned flaps in two ways: with the base to the mucoperiosteum and again with the base to the vomer.

With the former plan a red line appears in the hard palate, and although this tends to disappear with growth, the result does not have the appearance of a normal palate. In one case, the mucoperiosteal flaps were apparently in contact; the palate was competent to manage fluids, but soft foods appeared at the nostril. At redissection, a complete tube of mucous membrane extending from the root of the vomer up to and into the nose was found. The secondary repair was easy because the mucoperiosteum was in contact but not united. The flap with the base to the vomer is dove-tailed under the mucoperiosteum, seems to lessen the space between it and the bone, holds the mucoperiosteum in place and is greatly to be preferred to the other form.

Delayed Flap: In no case was a turn-over flap, either immediate or delayed, used. In adults or older children this has been used with average success to close holes present through loss of tissue. Early experience with it as a primary procedure was so disheartening that it has been put aside.

Occasionally, as a trial, the front ends of the flap have been cut and the flaps replaced, to be raised and sutured later. The tubulation and retraction have led to a large hole anteriorly, and to the exposure of the septum (fig. 26 *B*, lower cast). Something must be done to prevent this occurrence, and the best thing is the use of the vomer flap with the base to the bone and dove-tailed underneath, which anchors it in place. Even with this method, I have seen cases with a hole in front. I believe that some front attachment, however slight, should be maintained.

The plan of early secondary suture of the delayed flap has yielded the best results, when it can be followed.

The statistics show that the chance for primary complete union in the hard palate is the lowest offered by any suture line in the body. However, if the holes shown in figure 28, and the hole in front which

Fig. 28.—*A*, a linear hole which resulted after repair of a Group II–⅞ cleft. *B*, a round hole which resulted after repair of Group III left complete cleft. The hole at the alveolar process cannot be illustrated, but this has been included in the statistics of result under the general head of failures.

cannot be shown, are excluded, possibly my results are not bad when all the factors inimical to a clean wound are considered.

In spite of the report, I still believe that the Warren-Langenbeck principle is acceptable for three reasons:

1. From the study of the embryology, it is the only plan which purports, partly at least, to follow the natural formation of the hard palate.

2. When a primary unit is obtained, the result looks like a normal palate.

3. There is a high percentage of success in secondary repairs.

The trend more recently is to consider the proper season for operation, to inspect the child very carefully, to employ a sequence of operations in the wider clefts and the simplest procedure in the general run of cases with a wide, lateral incision and to give more care and attention to replacement of the flaps, thus taking the two-to-one chance of primary success.

Cleft of the Soft Palate.—The statistics on cleft of the soft palate follow:

Incidence of cleft of soft palate	278, or 77.4% of 350
No. of cases in which operation was done	207
No. of failures	7, or 2.43% of 207
No. of secondary failures	1

It is a great relief to come to the soft palate after the many problems of the other clefts and the great diversity of opinion concerning the steps in their repair.

All patients in this series have been operated on with the idea that the surgical principle is one of muscle repair.

In the literature all operations are based on this principle except one, which fails to recognize that muscle elements disturbed in their

Fig. 29.—*A*, the classic incomplete failure of operation on the lip: a notch at the nostril, a notch at the vermilion border and a short lip, due, I believe, to incomplete union of the musculature of the lip. This photograph is placed here to illustrate my idea that failure of the soft palate to develop may be explained on similar grounds and to emphasize my belief that the problems of the soft palate and of the body of the lip are alike; the prime efforts at repair should be directed to the active elements of those structures. *B*, the results of secondary repair made by the muscle theory operation.

normal relation of origin and attachment must lead to odd or incomplete action and disturbed function.

Excluding this suggestion, all others propose to unite medially and precisely the two halves of the soft palate with the great end in view of normal action of this structure for the purpose of speech and deglutition.

I believe that the many plans attain this result and that they are not different operations but different ways of doing the same thing.

The more recent literature offers some thrilling presentations and discussions on the anatomy, physiology and mechanics of the soft palate.

A new (to me) term of description appears—palatopharyngeal sphincter—which is so apt to the problem, that I believe it should be accepted and incorporated in the literature.

In all my cases the effort has been to repair the soft palate as it was found, in the belief that it was not the length of the palate that was

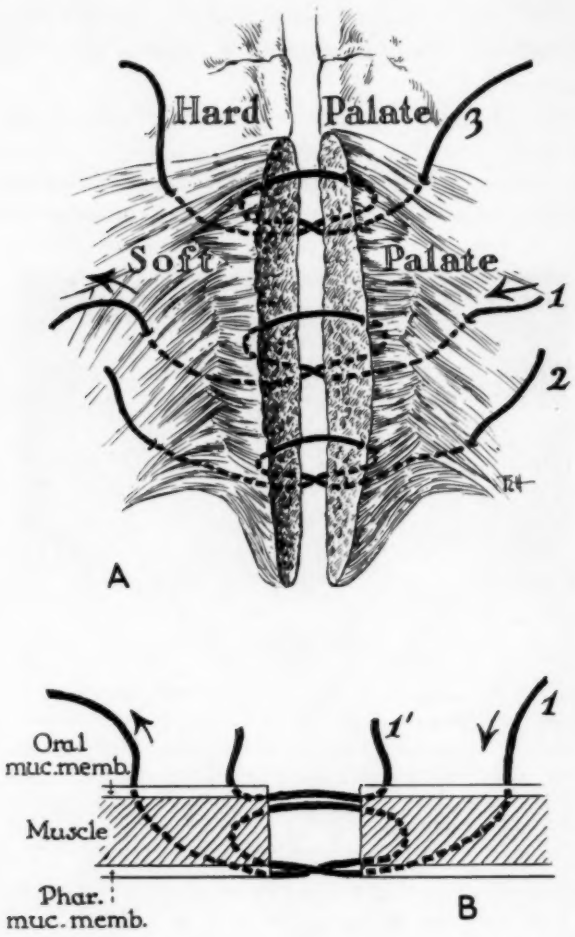


Fig. 30.—Operative procedure used on all soft palates in this series showing three end-on figure-of-eight stitches, supplemented by single stitches in the mucous membrane. The only change in the original plans is in the sequence of insertion. The first stitch is placed in the middle of the palate where a large body of tissue allows deep and positive bites of the suture and can be used as an anchor for the further handling of the palate. The second stitch is placed with the small loops at the top of the posterior pillars. This procedure brings into bold relief the tissues in the position of the tensor palati, where the third stitch is carefully inserted.

required, but complete and normal action, in order to repair a congenital cleft in a great muscle scheme, which included not only the constrictors of the throat, but those that were indirectly involved down to the larynx.

In fact, the broad general surgical principle in the repair of the body of the lip and the soft palate cleft are considered identical, and each defect is repaired with practically similar operative steps: in the lip, to allow the infant to develop its individual facial expression; in the palate, for control of motion, and in both areas, to coordinate general muscle action. Surgically, the prime effort is precision.

No effort to supplement length has been used because of the belief that if early motion is obtained by a successful union of the sides, the palate will grow along with the body, because the one thing that is known about muscle is that it hypertrophies on use and atrophies on disuse. Failure of the soft palate to develop is most often due, I believe, to inaccurate or incomplete contact of the muscle elements—a situation quite similar to the condition of the lip as shown in figure 29 *A*.

The technic in all cases is illustrated in figure 30 and is briefly discussed in the legend, in which particular attention is called to the slight modification of the sequence of stitch insertion.

The statistics show that the stitches held in 97 per cent of the operations on the soft palate. When one considers all the factors inimical to the primary repair, this is a high percentage, so high that the charts were rechecked. I know that a failure in repair of the soft palate comes as a surprise.

In the 7 cases of operative failure, there are 2 which show loss of tissue. This is a catastrophe, irreparable in most cases, and quite a different effect from a similar result in the hard palate. In the latter, the loss is usually replaced; in the former, secondary efforts have been either unsuccessful or incomplete.

Even though this percentage of success may be exaggerated, it is really high enough for one to say that the question of principles and procedure in repair of the soft palate approaches solution.

CONCLUSIONS

When one considers the time, thought and meticulous care expended on these babies and children, there is a great temptation to view the results through rose-tinted glasses. What I have said in relation to the results obtained in the repair of cleft lips, I wish to repeat in regard to the repair of the other clefts: that the percentages of my successes and failures would be materially altered by the criticism of my colleagues.

The study of these cases reveals that the most satisfactory fields are in the soft palate and the body of the lip. It must be noted that

in each position there are tissues with a wonderful faculty of compensation, and because of this many surgical errors may have been corrected.

The percentage of successful primary results of the operation on the hard palate cleft and the plastic reconstruction of the nostril of the unilateral lip is too low, but I feel that attention to some details of the paper will effect improvement in the future.

The most debatable and unsettled problem is the use of direct force other than pressure with the thumb in the alveolar process cleft. The possible penalty of the use of wire is overcorrection or misplacement and malocclusion. With all the care that I have taken with this possible result in mind, I am free to illustrate my extreme failures. The action of the indirect force of the lip may not close the alveolar process cleft, but the balance is enormously in favor of this plan, because it may easily be supplemented by a prosthesis, while by the use of wires the patient may be subjected to an elaborate follow-up treatment which could have been avoided.

However, the lip may not close the alveolar process in the wider clefts, and the routine use of this force irrespective of degree seems to me to avoid the issue. The answer to this problem probably lies in the age of the patient and an operation, even as a separate procedure, as early as possible in an effort to eliminate the use of wires in favor of the wonderful indirect force of the lip action.

I repeat that the alveolar process cleft is the most important in this field, to be elevated to a peak of consideration as to the age of the patient and the sequence of procedure and of operation in any case.

The statistics reveal that in all cases the clefts of the lip and alveolar process have been operated on at a stated time, i. e., early. Of patients with clefts of the hard and soft palates, only about three fourths have been operated on, which is explained by the more careful selection according to age, degree of cleft and other considerations.

The classification recognizes the importance of the cleft of the alveolar process. In Groups I and II the problems run fairly true to form, but in Group III is added the question: What shall be done to the bone cleft? The classification thus requires the exact literal and pictorial answer to the most important question: What kind of case is it?

Finally, I have found this work the most interesting, intriguing and fascinating of any field of surgery that I have ever studied. The responsibility assumed in the attempt to repair these congenital deformities is quite comparable to that imposed by the major operations on the body, and worthy of the attention of any surgeon. Yet with all this experience and intensive study, I believe with deep humility that there are still many problems that await the touch of a master hand.

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ANATOMIC BASIS FOR THE STUDY OF SPLANCHNOPTOSIS

THE PATHS OF VISCERAL DESCENT; A PRELIMINARY REPORT

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BOSTON

EN MASSE DESCENT OF THE VISCERA

In ptosis en masse, the abdominal visceral mass moves downward and forward, pushing the incompetent walls before it, without at first causing much change in the interrelations of the viscera, except that the more movable organs tend to descend farther and more rapidly than the less movable ones. This process is seen in its simplest form with the subject lying in the recumbent position when the descent of the diaphragm is insufficiently antagonized (fig. 4, *c*, in a preceding paper [1]).

In the supine position gravity acts in a ventrodorsal direction, and, for a time, offers an obstacle to mass descent, since it tends to hold the viscera toward their attachments to the posterior wall of the abdomen, while at the same time it reenforces the retaining powers of the anterior abdominal walls (fig. 1 *A*). In the lateral recumbent position the direction of the action of gravity is so changed that it becomes an additional factor which favors the development of varying phases of both ptosis en masse and individual splanchnoptoses, as well as changes in the body form (fig. 1, *E*, *F* and *G*).

But as soon as the trunk is erected from the horizontal to the vertical —as in changing from the supine to the sitting or standing position—the element of gravity (and its concomitants, traction and pressure) changes from a ventrodorsal to a cephalocaudal direction, and introduces pronounced visceral changes in the incompetent abdomen, regardless of the action of the diaphragm just noted. The retaining power of the abdominal walls is additionally weakened by this new factor, so that the walls themselves all tend to move downward and forward, and to exert traction or pressure in these directions on some of the viscera and on all the rest of the body form (in fig. 1, compare *B*, *C* and *D* with *A*; compare fig. 2, *d*, in a preceding paper [1] with fig. 3, *a* and *f*, in another paper,[2] showing the same child).

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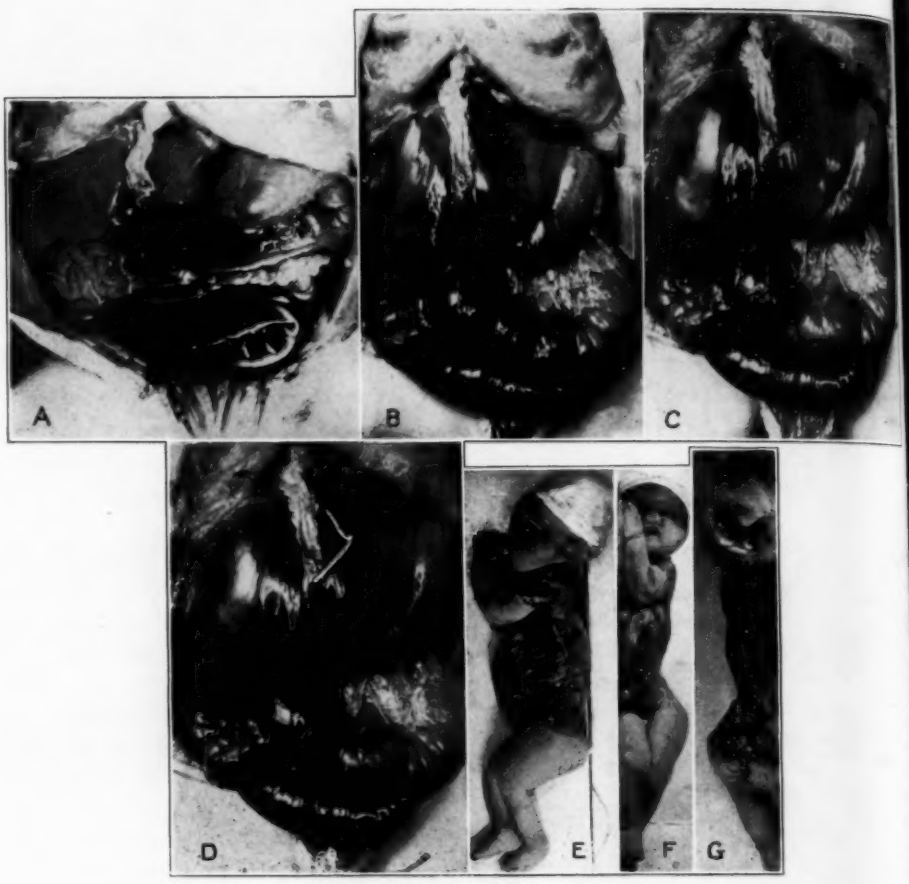

Fig. 1.—The paths of visceral descent due to unantagonized gravity, as the trunk is erected from the supine position to the vertical, in the child at term: *A*, supine position; the attachment of the falciform ligament of the liver to the wall of the upper part of the abdomen is left intact; the stomach is in the second stage of distention; the transparent great omentum is seen thrown upward, veil-like, across the lower half of the transverse colon. *B*, second sitting position (Vietor, A. C.: New England J. Med. **206**:1137 [June 2] 1932). *C*, flexed standing position. *D*, extended standing position. In *B*, *C*, *D*, note the progressive retraction of the walls of the thorax and the forward swing of all the abdominal viscera, the traction on the falciform ligament, the descent and swing to the right of the stomach (its development of the pipe bowl shape being hidden by the left lobe of the liver [fig. 4, *E*]), the descent of the spleen (visible to the left of the stomach and descending in a tongue-shaped process over the splenic flexure) and the traction on the stomach by the descending transverse colon, the stress being shown conveyed along the vessels of the gastrocolic ligament. *E*, *F*, *G*, marked ptosis en masse in the lateral recumbent position in a child at term, showing the resultant changes in the body form. *E*, view taken from above. *F*, view taken from in front. *G*, view taken from behind.

Moreover, as soon as the upper and lower extremities begin the stretching and elongation of the vestigial, biologically contracted deep fibrous tissues which bind them to the trunk, one of the first results is an increased sacrolumbothoracic anterior convexity which rotates the pelvis forward and downward, projects the viscera forward, causes stress on the abdominal walls and favors descent of both the walls and the viscera.[2] These changes begin in the supine position (Vietor,[2] fig. 2, *i*), but reach their maximum in the extended standing position (Vietor,[1] fig. 3, *a*).

Finally, all positional changes in the abdominal viscera are, sooner or later, reflected in the thoracic viscera and in the body form (fig. 3, *D* and *E*).

Traction on and by the viscera is largely exerted through peritoneal folds, between the layers of which run the visceral blood and lymph vessels and the visceral nerves. When the viscera are in their normal relations, these peritoneal folds are folded up and relaxed (fig. 1 *A*), but when the individual viscera are displaced, the folds tend to become opened out; traction then tends to be exerted directly on the visceral vessels and nerves, and thence to be conveyed distally to the visceral masses and proximally to the larger vascular trunks and to the larger neural trunks and ganglions (fig. 1, *B*, *C* and *D*). Traction tends to cause both arteries and veins to elongate and to diminish in caliber, the veins tending to flatten and collapse owing to their thinner and less resistant walls. And one has at present the known sensory effects of traction on the mesenteries in the opened abdomen and also the sensory, motor and trophic effects of traction on external nerves to guide one in questioning as to the more subtle, but undoubtedly far-reaching, effect on the visceral nerves and ganglions. The vascular changes are striking when in the child at term pressure and traction are seen to be especially exerted on the abdominal aorta and ascending vena cava by the unantagonized sacrolumbar anterior convexity which is suddenly developed by changing the lower extremities (thighs) from their spontaneous position of flexion, abduction and outward rotation to the advanced human position of extension, adduction and inward rotation so that the patellae look forward.[2] Such vascular interference, even if occurring slowly enough to permit of gradual changes in growth, suggests a causative factor in the more or less marked general nutritional changes which so often tend to occur in cases of ptosis en masse of the gravity type (Vietor,[1] fig. 3, *b*).

DESCENT OF INDIVIDUAL VISCERA

The most easily displaceable individual viscera are the kidneys, the stomach, the redundant portions of the colon, the liver, the lungs and the heart.

DESCENT OF THE KIDNEYS

In ptosis of the kidneys these organs, and the suprarenal glands to which they are attached, are projected forward from the depths of the paravertebral fossae to enter on the lumbo-iliac inclined planes which have a more or less steep ventrocaudal direction. Then the kidneys begin their independent descent, the suprarenal glands remaining behind but elongating and showing evidence of stress from the continuing traction exerted by the descending kidneys.

All the laterally placed viscera tend to lie in the long paravertebral fossae, but in ptosis en masse the shape and capacity of these fossae become modified by the descent of the viscera and the synchronous retraction of the posterior and lateral walls of the body.[1] From the broader central region of the trunk, these fossae narrow more or less as they continue downward. They also change their direction, passing ventrocaudad in an inclined plane to terminate at the level of the fourth or fifth lumbar vertebra, though their continuance into the iliac fossae is more or less suggested, especially when the pelvis is rotated backward. These lumbo-iliac inclined planes are strongly marked mediad by the forward projecting bodies of the related vertebrae, the masses of the psoas muscles and the medial portions of the quadratus lumborum muscles, structures which form the median boundary of the so-called kidney niches (fig. 2 *A*, *a*, *b* and *c*).

Owing to the relative shortness of the lumbar spine and to the relatively larger size of the kidneys at term, the lower poles of these organs at this stage of development lie only a little above the posterior crests of the ilia.[3] As a result, the kidneys lie more or less on these lumbo-iliac inclined planes which are directed more or less ventrocaudad in proportion as the pelvis is rotated forward or backward (fig. 2, compare *A* and *B*). As the child grows, the lumbar spine lengthens, and the kidneys appear to ascend (though their upper poles remain at the same level), thus resting higher and higher on the lengthening lumbo-iliac planes, the inclination of the latter decreasing from below upward. Thus the kidneys enter more and more into deeper parts of the paravertebral fossae, and they also rotate more and more backward and mediad on a relatively longitudinal axis, so that they come to lie a little obliquely, the hilus and its structures remaining the more anterior. Hence, other things being equal, the greater the breadth and depth of the paraver-

3. Vietor, Agnes C.: (*a*) The Fundamental Cause of Splanchnoptosis—Abdominal Incompetence; a Developmental Factor. A study of Certain Details of the Prenatal Evolution of the Abdomen, with Special Reference to the Status at Term, Bull. Lying-In Hosp. New York **12**:139, 1923; **13**:1, 1924; (*b*) The Anatomical Basis for the Study of Splanchnoptosis; the Abdominal Viscera at Term, Surg., Gynec. & Obst. **43**:293, 1926.

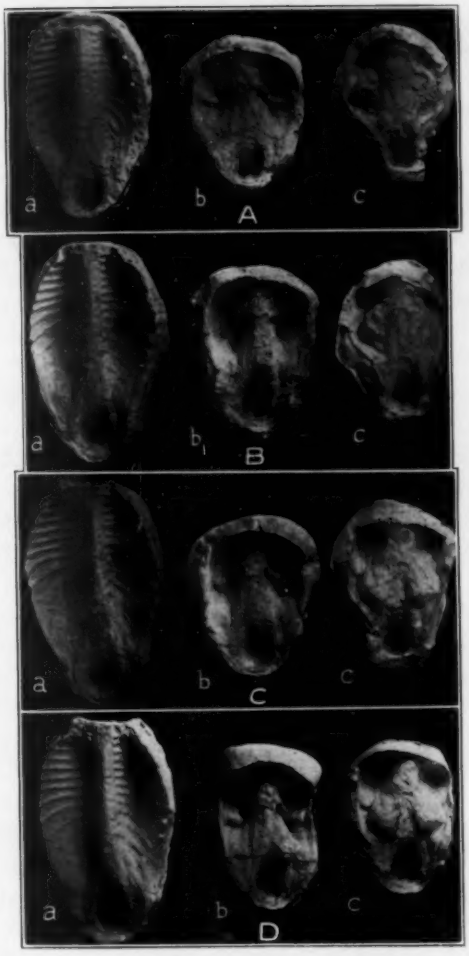

Fig. 2.—The paths of descent of the kidneys due to unantagonized gravity, as the trunk is erected from the supine position to the vertical, in the child at term: *A*, supine position, the lower extremities in spontaneous flexion, abduction and outward rotation. *B*, supine position, the lower extremities extended, adducted and rotated inward so that the patellae look forward; *C*, flexed standing position. *D*, extended standing position. In *B* and *D*, note the marked tension of the psoas iliacus muscles, the forward projection of the lumbar vertebrae, the forward rotation of the pelvis and the consequent forward thrust of the kidneys and suprarenal glands; *a* indicates the paravertebral fossae, showing the lumbo-iliac inclined planes and the basic foundation for the so-called kidney niches; *b*, the so-called hepatic, gastrosplenic and kidney niches and the lumbo-iliac inclined planes after removal of the kidneys, the suprarenal glands being left in position; the diaphragm is in the position of expiration, the domes sagging a little at their lowest parts; *c*, progressive stages in the descent of the kidneys as the lower extremities are extended, adducted and rotated inward so that the patellae look forward and as the trunk is erected from the supine to the standing position.

tebral fossae (reflected externally in the loins), the greater is the security of the kidneys in their position, and conversely.

But even at the greatest height and depth attained by the kidneys, the lumbo-iliac inclined planes offer ever ready paths favoring the descent of these organs. The extension cephalodorsad and the downward and forward inclination of these inclined planes are controlled largely by the sacrolumbothoracic anterior convexity which follows, more or less, the normal evolution of the lower extremities (thighs), as these pass from the position of flexion, abduction and outward rotation, existing at birth, to the more advanced human position of extension, adduction and inward rotation so that the patellae look forward.[2]

Even in the supine position, this anterior convexity (lordosis) is thus developed in proportion to the persistence of the vestigial contractions binding the extremities to the trunk, through failure of the postnatal antagonizing mechanism. And as it develops, the psoas iliacus muscles become tense and are thrown into strong relief; the loins are narrowed and dragged forward, and the pelvis is rotated forward and downward; the ventral inclination of the lumbar end of the lumbo-iliac inclined plane is increased; the base of the so-called renal "niche" is lifted as the twelfth and eleventh ribs become part of the inclined plane and as the paravertebral fossa shallows and narrows; while the kidney is rotated forward from without inward, is projected forward as a whole and, especially in its lower portion, now lies definitely on the always present lumbo-iliac inclined plane (fig. 2, *B*, *a*, *b* and *c*).

When the trunk is erected to the vertical (sitting or standing position), thus changing the action of gravity from ventrodorsad to cephalocaudad, the latter factor alone, unless the compensating mechanism develops equally, may now begin or accelerate the actual descent of the kidneys (fig. 2, *C* and *D*). Hence, ptosis of the kidneys, either alone or as a part of ptosis en masse, may begin in the recumbent position (fig. 1, *e*, *f* and *g*; Vietor,[1] fig. 4, *c*) or in the first sitting position (Vietor,[1] fig. 2, *a* and *b*), and it tends to increase, with increase in the conditions favoring it, through the second and third sitting positions (Vietor,[1] fig. 2, *c* and *d*) and through the standing positions (fig. 2, *C*, *a*, *b* and *c*), tending to reach its maximum in the extending standing position (fig. 2, *D*, *a*, *b* and *c*).

The preparatory step in the production of nephroptosis in even a normally placed kidney is, then, a forward projection of the kidney which lifts it out of its so-called niche in the paravertebral fossa and places it directly on the lumbo-iliac inclined plane. This preparatory step may be accomplished without disturbing the interrelations of the kidney and the suprarenal gland (fig. 2, *A* and *B*), since both the suprarenal glands and the kidneys are projected forward by the same factors, i. e., by increased anterior convexity of the lumbar spine (lordosis) and

by insufficiently antagonized descent of the diaphragm, these two factors acting separately or in combination.

The essential step in nephroptosis is separation of the kidney from the suprarenal gland and independent descent of the former, leaving the latter attached to the diaphragm and other structures. Normally, there exists a relatively loose combination of posterior peritoneum, fascial envelop and fatty envelop, within which the kidney has always some motion, and it is in connection with these tissues (from which it makes a ptosis pouch) that it can slide easily and extensively, downward and forward on the lumbo-iliac inclined plane, into varying degrees of ptosis (fig. 2, *C* and *D*). As the kidney is projected forward, it reverses its earlier backward and mediad rotation, the hilus becoming less and less relatively anterior. And in proportion as it separates from the suprarenal gland it rotates downward and outward, changing the direction of its long axis to downward and inward so as to approach, or even reach, the horizontal, and stretching and elongating the structures of its hilus and its connections with the suprarenal gland, on all of which it exerts traction.

EXPERIMENTAL DATA

Experimental Development of Nephroptosis.—Nephroptosis of the diaphragmatic type can be developed experimentally in the supine position within a few minutes, either in connection with ptosis en masse or individually. In the former case, the abdomen is not opened, and all the viscera remain in situ, the abdominal walls in the dead subject being incompetent within the limits of their fibrous tissues; under such circumstances, only the end-results can be demonstrated (Vietor,[1] fig. 4, *c*). In the latter case, the abdomen is opened and the other viscera are removed so as to expose the undisturbed suprarenal glands and kidneys; the various steps can then be studied in sequence, as they progress to the same end-results, respiration being simulated by intermittent inflation of the lungs.

As the insufficiently antagonized diaphragm descends more and more deeply under pressure of the intermittently inflated lungs (which continue to hold more and more residual air), the suprarenal glands are drawn forward and upward on the pillars of the diaphragm to which they are attached, and they are seen to pucker all over in moderately fine puckerings which seem to involve the entire depth of their substance. The kidneys follow the suprarenal glands forward, and as they are thus projected, they reverse their earlier backward and mediad rotation, and the hili become less and less relatively anterior. At the same time, the kidneys move downward and outward from the suprarenal glands, being pushed in these directions by the elastic pressure of the descending domes of the diaphragm against their upper poles. Thus, as they descend, they rotate downward and outward as on a relatively anteroposterior axis, the upper poles diverging and the lower poles converging. Coincidentally, the kidneys exert pressure and traction on their enclosing structures, so as to produce ptosis pouches; the process is similar to that occurring in the gravity type of ptosis, which is to be described next, though in a lessened degree. These processes continue until the kidneys are so far detached from the suprarenal glands as to be no longer within reach of the pressure of the descending diaphragm, when the direct action of the diaphragm

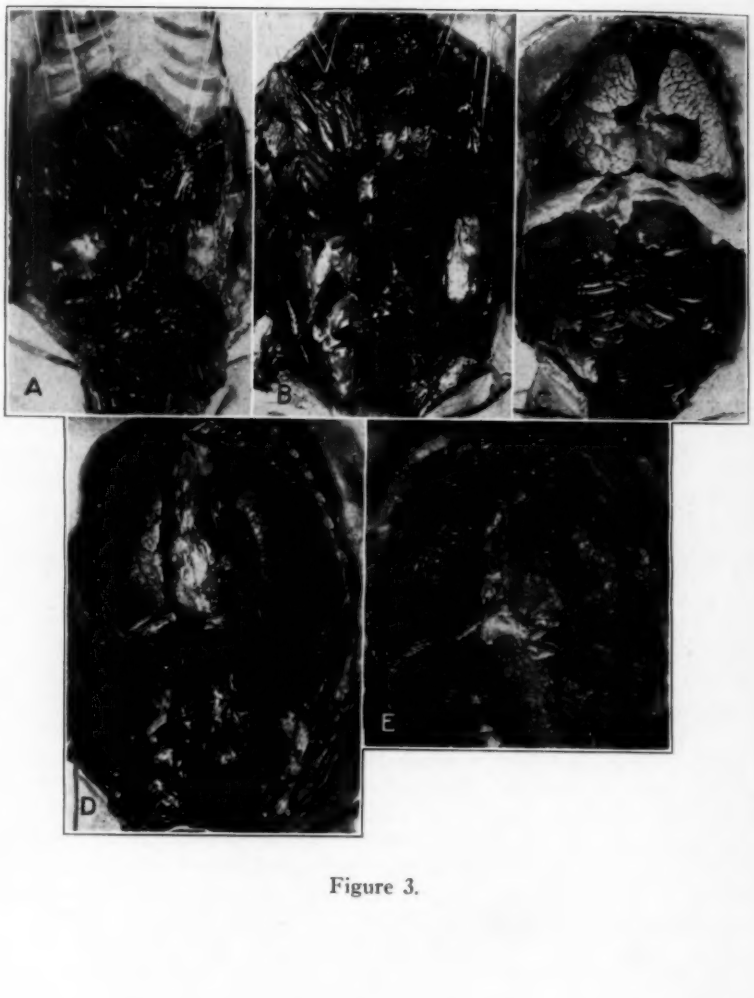

Figure 3.

EXPLANATION OF FIGURE 3.

Fig. 3.—Details of intermediate stages in ptosis of the kidneys: *A*, ptosis of the kidneys as part of ptosis en masse, showing the displacement more marked in the right kidney than in the left. The liver, stomach, and left portion of the transverse colon are held up by mattress sutures to reveal the kidneys in situ. The right kidney is largely separated from the suprarenal gland and is rotated downward and outward so that its long axis approaches the horizontal. The traction exerted on it by the ptosed right portion of the transverse colon and the overlying pressure exerted by the liver are clearly shown. The left kidney is just emerging from beneath the suprarenal gland, and its long axis has begun to be directed obliquely downward and inward, while its freedom from direct traction and pressure contrasts strongly with those factors on the right. *B*, all the abdominal viscera are removed except the liver, the suprarenal glands and the kidneys. The liver is then drawn upward, pulling the suprarenal glands and the kidneys upward and forward, and throwing into strong relief the ptosis pouches formed by the descending kidneys as they separate from the suprarenal glands, pushing before themselves the posterior peritoneum and the anterior portions of their fascial and fatty envelops. The kidneys have been freed from their adhesions to the suprarenal glands and to the pouches, to show the more advanced stage of ptosis when they hang suspended from the structures of their hili (compare with *D*). Their long axes are now practically horizontal, and their lower poles overlap in the median line. Note the flattened, triangular, tongue-shaped continuations of the posterior perirenal and pararenal fat, which slide downward behind the posterior peritoneum. Note also the ptosis of the lungs and of the heart: *C*, supine position; view taken from above. The thoracic and abdominal viscera are in position, as found at term, the lungs being artificially inflated to counteract the retraction ensuing on opening the pleural cavities. The transparent, veil-like structure thrown over the transverse colon is the great omentum. *D*, extended standing position, view taken from in front. The kidneys were displaced as a part of the gravity type of ptosis en masse. Then the other abdominal viscera were removed; the ptosis pouches of the kidney were opened, exposing their interiors, and the kidneys were freed and allowed to descend as far as the structures of their hili permitted. The thorax was then opened, and the heart and lungs were found displaced and showing the changes characteristic of advanced ptosis en masse of the gravity type. The pericardium was not opened. Note the marks of traction shown by it, by the mediastinal tissues and their extensions upward and by the thymus. Note that the left lung tends to fall lower than the right, to a greater or less degree. *E*, same subject as in *D*. No change was made except to lower the subject to the supine position, thus changing the direction of gravity from cephalocaudal to ventrodorsal (view taken from above). The right lung is displaced from in front to show how the posterior border expands medially, thus helping to hold the heart forward. Otherwise, there is return of the heart and lungs to approximately their original conditions, with disappearance of the evidences of traction and stress. Note the returning shortening and broadening of the thoracic cavity and its viscera, as well as of the abdominal cavity. Note the return of the kidneys and of the elongated and stretched suprarenal glands toward their original positions.

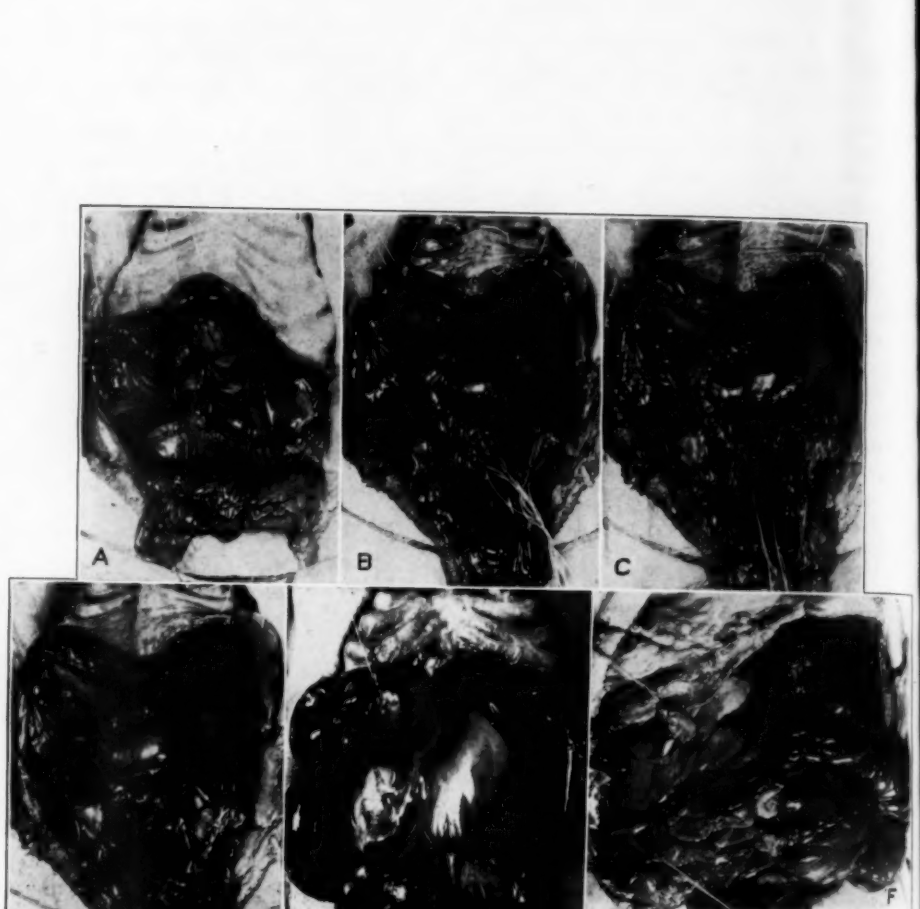

Figure 4.

Explanation of Figure 4.

Fig. 4.—The paths of descent of the stomach, in varying stages of distention, when exposed to insufficiently antagonized gravity in the extended standing position. *A*, the stomach is in the second stage of distention, and it has already descended. Note the narrowing and elongation as the cardia is approached, the accompanying descent of the narrowed and elongated spleen to the left and the traction by the descended transverse colon on the body and antrum of the stomach, the first portion of the duodenum, the transverse fissure of the liver and the neck of the gallbladder. The gastrocolic ligament became detached from the stomach between the vertical wrinkle shown and the point of contact of the left border with the spleen. Note how the persisting traction to the right of this area interferes with the normal upward and forward rotation of the stomach which begins in this stage (compare with *E*, and note how traction on the stomach by the transverse colon is lessened, as in this case, when the latter is empty and when it finds support, as on the cushion of distended small intestines). *B*, in addition to the liquid present, the stomach is inflated with air sufficiently to carry it to the beginning of the third stage of distention, the edge of the left side of the thorax being lifted by a suture to show the gastrosplenic niche. Note the migration of the stomach downward, forward and to the right, as well as the marked rotation upward and forward and the kinking on both the gastric and duodenal sides of the pylorus, while the outlines of the antrum tend to merge more definitely with those of the body and to suggest a form of telescoping of the former into the latter. *C*, inflation is carried further, so as to develop a later phase of the third stage of distention, the stomach migrating still farther downward, forward and to the right, the antrum moving toward assuming an anteroposterior direction, and the first portion of the duodenum moving toward kinking and torsion, as it becomes hidden by the antrum and body of the stomach. Note the increased descent of the spleen as it lies on the splenic flexure. *D*, inflation is carried still further so as to develop the fourth stage of distention, the stomach approaching the limits of its migration downward, forward and to the right, and adding a second upward and forward rotation. The antrum is directed backward, or even a little from right to left, and it tends to press the pylorus or the adjacent part of the first portion of the duodenum against the posterior wall of the abdomen, and to cause obstruction of the stomach or duodenum, or of both. The spleen continues to move downward, forward and to the right with the stomach. In this case, the low density of the distending contents partly antagonizes the localizing effect of gravity, the stomach falling more gently throughout, in contrast with the stomach in *E*. *E*, same subject as in figure 1, *A* to *D*, in which the stomach contents are of greater density. The liver is held up to reveal the stomach which shows that the effect of gravity is not only diffused generally, but is especially localized in the lowest part of the body of the stomach, the tissues yielding and developing the pipe bowl shape of stomach, and impairing the upward and forward rotation belonging to this stage of rotation (second to third). Note the kinking at both ends of the antrum (which maintains its direction upward and to the right, due in part to the frustration of this upward and forward rotation. *F*, the liver is experimentally rotated backward and to the right, causing descent of the transverse fissure, the lesser omentum, the antrum and the first portion of the duodenum and developing an approach to what has been called the "tubular" type of stomach. The experiment is favored in this case by the pressure of a distended large loop of the subgastric transverse colon which nearly fills the left hypochondrium by displacing the stomach into, or to the right of, the median line. Note the greater visibility of the transparent great omentum in this case, as compared with figure 1, *A*, owing to the greater deposits of fat along the lines of the blood vessels.

on the kidneys ceases (Vietor,[1] fig. 4, *c*). As the kidneys descend, they make traction with each inspiration on the connections uniting them with the suprarenal glands, this traction being conveyed to the latter organs through their fibrous framework, and producing the puckerings seen externally. If the lower extremities (thighs) are first extended, adducted and rotated inward so that the patellae look forward, the consequent forward projection of the lumbothoracic spine, the kidneys and the suprarenal glands, facilitates the separation of the kidneys from the suprarenal glands.

Nephroptosis of the gravity type can be developed experimentally a little less speedily but, nevertheless, quite rapidly (fig. 2, *A, B, C* and *D;* fig. 3, *A, B, D* and *E;* fig. 4, *A* and *E*). In addition to gravity acting in the downward and forward direction of least resistance, the initial force from behind to project the kidney forward is in this case not the diaphragm, though this element may be added, but the sacrolumbothoracic anterior convexity which tends to develop as the trunk is erected to the vertical, and which is increased in the extended standing position as the lower extremities are at the same time extended, adducted and rotated inward so that the patellae look forward. Both the suprarenal glands and the kidneys are carried forward, the latter again rotating forward and mediad and also descending and making traction on the former, but the traction is now continuous instead of intermittent, and instead of puckering the suprarenal glands it causes them to elongate and to be dragged after the descending kidneys. This causes traction stress on the suprarenal glands which is conveyed through them to their basic attachments to the diaphragm and other structures, but these attachments do not yield, and the suprarenal glands remain in their relative position.

As the kidneys become separated from the suprarenal glands and descend, they also begin to rotate downward and outward as on a relatively anteroposterior axis, the upper poles diverging and the lower poles converging. Thus, the long axis of the kidney, from being directed downward and outward, becomes first vertical and then inclined more and more obliquely downward and inward, as it moves toward the horizontal, eventually approximating, or even reaching, that position.

As the kidney moves caudad, away from the suprarenal gland, it pushes before itself the anterior leaf of its fascial envelop (covered in part by the posterior peritoneum) as well as the related portion of the perirenal fatty envelop, and it thus develops a pouch in which it lies, this ptosis pouch gradually broadening below and collapsing above as the kidney descends, still rotating outward as it descends, so that its long axis continues to move toward the horizontal. This pouch is sharply delimited laterally by the union of the anterior and posterior leaves of the perirenal fascia, and it is definitely delimited below, though the anterior and posterior leaves of the perirenal fascia do not here directly merge. They are, however, united to each other by a special arrangement of strong fibers of connective tissue which extend through the perirenal fat and form what has been termed a "basket" (Kelly and Burnam) below the lower pole of the kidney.

While the ptosis pouch of the descending kidney is thus formed largely by the stretched and elongated anterior leaf of the renal fascial envelop, with the related portion of the perirenal fat, the posterior leaf of the renal fascial envelop shares in the descent by elongating and sliding downward on the posterior abdominal wall without definitely leaving the latter. Hence, it is the posterior leaf which appears to be the stronger, either intrinsically or through its connections, or perhaps both. In any case, it bears the brunt of the traction exerted by the descending kidney, and, in turn, beyond the limits of its yielding to this stress, it transmits the traction to the posterior abdominal wall. The continuations of both the peri-

renal and the pararenal fat below the kidney also slide downward, forming two flattened, triangular, tongue-shaped masses of fat, with apexes directed downward, which advance below the descending kidney down the iliac fossa and along the lateral brim of the pelvis, pushing before them the overlying posterior peritoneum. These sliding triangles of fat are more or less sharply delimited from each other and from the mass of the descending kidney (fig. 3, *B* and *D*).

By combining the displacing action of unantagonized gravity in the standing position and that of insufficiently antagonized descent of the diaphragm, the complete cycle of nephroptosis can be developed experimentally in a very short time. It can be compared with the autoproduction of a demonstrable advanced nephroptosis in the unopened abdomen in the standing position in the following case: A tall, slender woman, aged 26, has ptosis en masse of the gravity type. She states that she had subjected herself to marked tight lacing for several years. During that time, her right kidney was said always to be prolapsed. Since her marriage, two years ago, she has given up lacing, and now the kidney is often not easily palpable. She can bring it into evidence by standing and throwing her trunk to the left side and backward, arching the left side of the trunk. This flattens the lumbosacral region and throws the right pelvis up and forward, flares the right lower ribs and makes the right side of the abdomen prominent. She then increases the intra-abdominal pressure by taking quick, deep abdominal inspirations and by making slow, forcible expirations, each accompanied by a downward expulsive effort concentrated toward the right side of the abdomen. As she proceeds, the right kidney emerges from beneath the liver and ribs and can be plainly followed by the hand as it travels down to the pelvis and backward and forward across the right side of the abdomen. The patient reports repeated attacks that answer the description of ureteral colic.

In the gravity type, if the ptosis pouch and other related structures are not too stretched and lax, the assumption of the supine position tends to encourage the kidneys to slide upward and backward, along the lumbo-iliac inclined planes, toward the suprarenal glands and toward the primary location of the structures of their hili (fig. 3, compare *E* with *D*). If the related structures are too lax thus to guide it, the kidney remains floating in some part of the abdomen, and it may, more or less, even cross the median line (fig. 3, *B* and *D*).

In the diaphragmatic type, the return of the kidneys in the supine position is hindered by the tendency of the diaphragm to remain lowered, even during expiration, owing to the tendency of the ptosed lungs to become emphysematous, and to the tendency of the diaphragm to become lowered, broadened and shallowed (Vietor,[1] fig. 4).

Intrinsically, the two kidneys, their envelops and their immediate attachments react in the same way to the same laws, but the right kidney tends to descend more easily and to a lower level than the left. This is the result of several extraneous factors: 1. The colonic and primitive mesenteric evolution of the right side of the abdomen takes place later than that of the left and, consequently, is less complete and stable; as a result of this condition, the colonic and primitive mesenteric surroundings of the right kidney give less stability and support, and permit more pressure and traction, which favor descent (fig. 3, *A*). 2. Other abdominal viscera exert a displacing power on the right kidney which they do not exert on the left, and a retaining power on the left kidney

which they do not exert on the right (fig. 3, *A*). 3. Some of the ultimate attachments of the right kidney are longer or less resistant than the corresponding ones of the left kidney, and some of the ultimate attachments of the left kidney are shorter or more resistant than the corresponding ones of the right kidney (fig. 3, *B* and *D*).

In all cases, when the other abdominal viscera are left in situ, the right kidney descends more easily and rapidly than the left (fig. 3, *A*). In all cases, when the other abdominal viscera are removed, and only the kidneys and suprarenal glands are left in situ but undisturbed, the two kidneys descend similarly, sometimes the left being momentarily the lower; but ultimately, when (on opening the enclosing pouches and freeing the kidneys from their adhesions to these pouches and to the suprarenal glands) the two kidneys hang swinging on the elongated structures of their hili, the right tends to hang lower than the left (fig. 3, *B* and *D*).

DESCENT OF THE STOMACH

In ptosis of the stomach, the fundus remains under the left vault of the diaphragm; the organ as a whole struggles to rotate upward and forward, and to migrate downward, forward and to the right, and conversely, as it is distended and emptied; the antrum remains high at its junction with the first portion of the duodenum, but eventually the walls of the body yield and descend below the level of the antrum to form the bowl of the typical "pipe-shaped" stomach.

EXPERIMENTAL DATA

The marked normal mobility and the varied positional changes observed in this study as the stomach passes from the empty to the distended condition and back to the empty or resting position have been described in detail.[3] It will suffice now to note that under distention the first change is the separation of the anterior and posterior walls from each other, the organ remaining in position (first stage of distention). Then, if the distention is continued and increased, the stomach balloons out in all directions and migrates from its recess (gastrosplenic niche of left paravertebral fossa) behind the left lobe of the liver and under the left dome of the diaphragm where, however, the fundus remains, the path of migration being determined by the inclined plane which bounds the gastrosplenic niche medially and antero-inferiorly. As it migrates, it rotates on varied axes, at first forward and upward (second stage of distention, fig. 4, *A*), then also downward, forward and to the right (third stage of distention, fig. 4, *B* and *C*), and, finally, again forward and upward (fourth stage of distention, fig. 4, *D*). Then, as its distention subsides, it passes through these changes in reverse order and retracts until it lies, with anterior and posterior walls in apposition, in its original location and in its empty or resting shape and position (Vietor,[3b] figs. 6 and 7). These physiologic changes of position and contour must be differentiated from ptosis, though the path of descent of the stomach in ptosis is largely determined by this physiologic basis.

All the hollow abdominal viscera have the common peculiarity that as they are distended they tend to swing on their mesentery and to rotate forward and upward, the degree of rotation (other things being equal) depending on the density of their contents, being greatest when this is least. A structure which in this sense acts toward the stomach as the regular mesentery does toward the intestines is the lesser omentum (gastrohepatic omentum or so-called gastrohepatic ligament), and it is on this peritoneal fold that the stomach swings in its normal movements of distention and retraction (though in the initial upward and forward movement, which is more definitely limited to the body of the stomach, i. e., in the second stage of distention, the rotation seems to occur more definitely on the abdominal esophagus and the gastrophrenic ligament, fig. 4, *A* and *E*).

And it is on this peritoneal fold, and on the structures which it encloses, that traction is markedly made when it is unfolded by the descent of the stomach in ptosis. The distal attachments of this gastrohepatic mesentery are the central tendon of the diaphragm (from the neighborhood of the esophageal opening) and, passing to the right, the transverse fissure of the liver. The support of the stomach is continued to the left of this gastrohepatic mesentery by the abdominal esophagus, the gastrophrenic ligament and the gastrosplenic omentum, as well as by the direct (nonperitoneal) attachment of the cardia and fundus to the diaphragm; and it is continued dorsad by the great vascular trunks which run so short a course before being distributed to the stomach and related viscera. Traction by the descending stomach is exerted on all these structures, including the related nerves and ganglions.

The one outstanding factor in ptosis of the stomach is the relative resistance which this line of attachment offers to the traction exerted on it by the descending stomach, the tissues of the stomach themselves eventually yielding under the stress (fig. 4 *E*). It is important to note that the attachment of the lesser omentum is continued to the right beyond the limits of the antrum of the stomach, so as to include the first portion of the duodenum (fig. 4, *A, B* and *E*); the resistant powers of this and of related nearby structures are well shown by the observation that even in advanced gastroptosis the duodeno-antral region remains high, the firmer antrum suggesting a stem on which the flaccid body of the stomach hangs and sags, the body tending to elongate and to develop the familiar pipe-bowl-shaped stomach, with kinking tending to develop at one or at both ends of the antrum, i. e., in the softer body of the stomach or in the softer first portion of the duodenum (fig. 4, *B* and *E*). It is further important to note that when this duodeno-antral portion of the lesser omentum is unfolded and subject to traction, the latter force is expended also on the important structures which are enclosed within

its folds as they enter or emerge from the transverse fissure of the liver, i. e., the hepatic artery and vein, the bile ducts and the portal vein, together with lymphatic vessels and nerve plexuses (fig. 4, *A, B, C, D* and *E*). And when the cysticocolic ligament exists as an extension of the lesser omentum, the traction is thus extended to the neck of the gall-bladder (fig. 4, *A, B* and *C*).

Although the fundus remains under the left dome of the diaphragm, as the stomach descends traction is made on the abdominal esophagus, which tends to elongate and to narrow. There is a similar tendency to elongation and narrowing of the cardia and, indeed, of the whole body of the stomach, as a result of the traction which is thence conveyed to its diaphragmatic attachments (fig. 4, *A* and *E*).

The fundus and body of the stomach and the spleen lie in what may be called the gastrosplenic niche, in the sense in which the lungs, the liver and the kidneys lie in niches, all these recesses being parts of the paravertebral fossae (fig. 2, *A* to *D;* fig. 3, *C, D* and *E*). This gastrosplenic niche in its upper portion forms a more or less deep and broad concavity which lodges the spleen, the fundus and most of the body of the stomach (fig. 4, *B, C, D* and *E*), while its lower and more median portion forms an inclined plane which is directed downward, forward and mediad, and which consists of the left suprarenal gland and kidney, the left portion of the pancreas and, still more deeply, the posterior portion of the diaphragm separating the abdominal and thoracic cavities (fig. 2, *A, B, C* and *D*). It is on this inclined plane that the lower part of the body of the stomach and the antrum lie, though the latter may pass on or over the projecting front of the vertebral bodies to unite with the first portion of the duodenum. Above and on the left side, the gastrosplenic niche is bounded by the left lobe of the liver and by the left dome of the diaphragm, the splenic flexure of the colon and the transverse mesocolon being interposed below (fig. 4, *A* to *E*). On the median side the niche is limited by the vertebral column and by the posterior angles of the related ribs, being separated from these structures by the diaphragm and by the left pleural cavity, while the lesser curvature is continuous with the transverse fissure of the liver through the gastrohepatic omentum (fig. 4, *A, B, C* and *D*).

Not only is the stomach subject to descent through the influence of insufficiently antagonized gravity and descent of the diaphragm, which cause it to exert traction on its supporting attachments, but it is also subject to traction from below; this added traction tends to increase its descent and its former traction as well as the yielding of its own tissues. The added traction is due to descent of the transverse colon and is exerted through the gastrocolic ligament whenever this peritoneal fold is less deep than is the corresponding portion of the transverse mesocolon (fig. 1, *B, C* and *D;* fig. 4, *A, B* and *E*). Thus, another force is added toward producing gastroptosis, and particularly the pipe-bowl-shaped stomach (fig. 4, *A* and *E*). And as the subgastric transverse colon is always more or less redundant [3] (Vietor,[3b] table 1), traction by

it on the stomach, through the gastrocolic ligament, is always potential when the abdomen is incompetent.

In this study, the gastrocolic ligament at term has been found to vary greatly in depth (from about 1 mm. to practically the same depth as that of the transverse mesocolon), and this variation is not uniform in all portions, being deeper, for example, in the redundant loops of the subgastric transverse colon than in the nonredundant portions. It has also been found that, regardless of other redundancies of the transverse colon, the most constantly redundant loop tends to lie below the vicinity of the external border of the resting or empty stomach,[3] this redundancy seeming to be related to the normal excursions in mobility of the stomach as it passes from emptiness to distention and back to emptiness.

The So-Called Tubular Stomach.—In this study, descent of the duodeno-antral region occurred only when the liver was rotated backward and to the right, and this descent favored the development of what has been called the tubular type of stomach (fig. 4 *F*). This tubular appearance seemed more strongly suggested when the stomach was of the pyriform rather than when it was of the quadrangular type (Vietor,[3b] figs. 7, 9-XLVI and 5-XLIX).

Relation of the First Portion of the Duodenum to Movements of the Stomach.—The proximal part of the first portion of the duodenum is movable, and it shares more or less in the movements of the stomach, thus permitting the stomach to move farther to the right, or forward, or upward or downward, as it migrates during distention,[3b] and at the same time tending to produce kinking, torsions, or obstruction of the duodenum. As the stomach descends in ptosis, it still struggles during distention to pass through the cycle of changes described, but as it falls, there is a greater tendency to develop kinking at the junction of the body and the antrum, as well as kinking and torsion of the first portion of the duodenum (fig. 4, *B*, *C*, *D* and *E*), with increased tendency to develop obstruction at the pylorus or just distally to that point (compare fig. 4 *D* with figs. 7, 9-XLIIB and 9-XXXVII in a preceding paper [3b]).

CLINICAL QUESTIONS SUGGESTED

Remembering the marked tendency to the development of ulcer along the lesser and greater curvatures of the stomach, and on both the gastric and duodenal sides of the pylorus, one cannot help but question whether the traction on the regions here demonstrated may not at least predispose to the development of such lesions. Other things being equal, the gastric lesions would be expected to occur more often in the smaller eaters, whose stomachs would be more likely to be limited to the earlier phases of distention (the first, second, and early third stages), and who would be thus more directly exposed to simple insufficiently antagonized gravity and traction; while the pyloric and duodenal lesions should be more frequent in the larger eaters, whose stomachs would be more likely to pass through the more advanced phases of distention (the more advanced third and the fourth stages),

which tend more definitely to involve the region of the pylorus and the first portion of the duodenum in torsion, as well as in kinking, traction and obstruction.

Also, as one notes the ease with which obstruction of the stomach or of the first portion of the duodenum may be produced at term by overdistention of the stomach (the later third and the fourth stages [3b]), which causes the antrum, with or without the movable part of the first portion of the duodenum, to assume an anteroposterior direction and press the pylorus or the adjacent first portion of the duodenum against the posterior abdominal wall, one cannot but question whether a so-called "congenital hypertrophy of the pylorus" may not rather often be an acquired condition (fig. 4, *D*; compare with figs. 7, 9-XLIIA, 9-XLIIB and 9-XXXVII, in a preceding paper [3b]).

PTOSIS OF OTHER ORGANS

Spleen.—As the stomach descends, it makes traction on the spleen and exposes the latter organ more definitely to the action of insufficiently antagonized gravity. As a result, the spleen descends in a tonguelike process which extends downward to the left side of the descending stomach, apparently being guided by the sustentaculum lienis (left phrenocolic ligament) to slide on or over the splenic flexure (fig. 1, *B, C* and *D;* fig. 4, *A* to *E*).

Colon.—In ptosis of the nonredundant colon, this portion of the intestine tends to move downward, forward and mediad, making traction on, and elongating, its mesocolon or attachments, and tending to develop or to increase angulation, kinking and stasis. In ptosis of the redundant colon, the loops readily unfold, introducing at once the variable problems of migration and torsion; of traction on the vessels and nerves of their mesocolon and intervisceral connections, and on the continuations and attachments of these structures; and of kinking and stasis at the angles of the loops.

The nonredundant colon follows the lines of parietal attachment of its mesocolon in outlining, a little irregularly, the circumference of the posterior and posterolateral walls of the abdomen (Vietor,[3b] fig. 8). The redundant colon follows parietally the same lines of mesocolon attachment, but its mesocolon varies in depth and its redundant tissue forms loops (Vietor,[3b] fig. 9). These redundant loops are found in prenatal life and at term in one of two conditions: They are either more or less folded up along the lines of the parietal attachment of the mesocolon (fig. 1 *A;* fig. 3 *C;* fig. 4 *A* and *F*), or else they are more or less unfolded and directed, predominantly, toward the midabdomen (fig. 1, *B, C* and *D;* fig. 4 *E*).

Thus, an unfolded intestinal loop cannot necessarily be considered an example of ptosis. It would seem, rather, that ptosis might be considered to begin when the abdominal walls are so incompetent to support the unfolded loop, either directly or indirectly, that traction is exerted on the mesocolon or on intervisceral or parietal attachments.

Though migrations and displacements may at times cause some variation, the unfolded loops of the transverse colon tend to be directed downward; the sigmoid colon, upward; the subhepatic, downward, forward and inward; and the ascending and descending colons, forward and inward and perhaps also downward (Vietor,[3b] figs. 4, 5, 9 and 10).[3]

The position of the colon and its loops is also modified by the degree of support and counter-resistance offered by the abdominal walls, by the degree of distention which they undergo and by the density of the distending contents. When distended, the colon has a tendency to rotate on its mesocolon eccentrically to the midabdomen; in such case, the loops tend to migrate upward, or upward and outward, especially if the density of the contents decreases, though gravity tends to make them descend, especially if the density of the contents increases. Thus, the transverse colon may at any moment swing upward and be found projecting forward at any angle to the vertical; it may overlap the free margins of the right or left lobes of the liver, or it may even be found filling the left part of the hypochondrium, compressing the stomach, displacing it toward the right, and causing it to make lateral traction on the abdominal esophagus (fig. 4 *F*).

In the vertical positions (sitting, standing), gravity tends to cause the redundant loops of the transverse colon to fall downward and forward and toward the midabdomen; the loops of the sigmoid colon tend to fall and to become displaced (especially toward the right) and to form new arrangements,[3] and those of the ascending and descending colons tend to swing forward and downward.

As the transverse colon descends, it makes more or less traction on its attachment to the posterior abdominal wall and to the intervening viscera, either directly or through the transverse mesocolon, the former being especially characteristic of the right portion as it crosses the second portion of the duodenum and the right kidney (fig. 3 *A;* fig. 4 *A*). The left portion would similarly make traction on its mesocolon, but it tends first to make traction on certain intervening viscera whenever the intervisceral connections are shallower than is the transverse mesentery. These intervening viscera are the stomach, the first portion of the duodenum and the neck of the gallbladder, and the traction is made through the gastrocolic, the duodenocolic and the cysticocolic ligaments [3b] (fig. 3 *A*; fig. 4, *A, B, C, D, E* and *F*).

As the redundant loops are unfolded, kinking may occur at one or at both ends of the loops, interfering with both peristalsis and antiperistalsis and leading toward stasis. This tendency is modified in proportion as the angles at the ends are distended; hence traction, kinking, and stasis are most pronounced when emptiness of the angles coincides with fulness of the body of the loop (Vietor,[3b] figs. 4, 5 and 16).

The small intestine is surrounded by the large intestine. When the former is distended, it moves forward on its mesenteric anchorage and extends eccentrically in all directions, proportionately to the density of its distending contents and to other factors. It thus tends to exert pressure, eccentrically, on the surrounding large intestine and to form an elastic cushion on which rest the transverse colon and mesocolon, the liver and the distended stomach (fig. 3 *C*). If distention of the large intestine is added, the latter rotates further on its mesocolon, eccentrically to the midabdomen; the abdomen is enlarged in all directions, and the transverse colon may be found thrown upward over the liver and stomach, or encroaching on the latter in the depth of the left part of the hypochondrium, or even (if the gastroduodenocolic ligament is shallow enough) making upward traction on the stomach and first portion of the duodenum, and perhaps even on the neck of the gallbladder.

Liver.—In ptosis of the liver, this organ, like the fundus of the stomach, does not leave its position under the domes of the diaphragm; hence, as it descends under the influence of insufficiently antagonized gravity, the diaphragm, the walls of the thoracic cage and the lungs retract to follow it, the ribs becoming oblique as they fall, and all three of the latter structures diminish proportionately in lateral expansion during inspiration. These changes in the surroundings of the liver explain why its ptosis may not be confirmed by percussion of the parietes, since as the organ descends, the enclosing parietes also descend, at the same time retracting, especially laterally. Again, somewhat similarly to the body of the stomach, the tissues of the liver themselves may yield under stress, so that the organ may tend in time, wholly or partially, toward elongation and change in contour (fig. 1, compare *B, C* and *D* with *A;* note *E, F* and *G*).

The liver is held in position in apposition with the domes of the diaphragm not only by its attachments but also by a negative pressure resembling that noted in the articulations, and within the limits of its attachments it seems to move physiologically somewhat as does the head of the bone within a ball and socket joint. These movements are varieties of limited rotations on varied axes and have been called versions. The rotations may be forward, backward or laterally, or in combinations of these directions, and they seem to be in the nature of adaptations to the other viscera and to the parietes. The first change which the liver undergoes in ptosis is in the direction of more or less exaggeration of these physiologic movements. When the abdominal walls are relaxed, and even in the supine position, the liver tends to sag toward the right, in the direction of its heavier lobe, making more or less traction in that direction on all its connections, both visceral and parietal (fig. 1 *A*). This sagging to the right is increased in the right lateral recumbent

position (fig. 1, *E* and *F*), but it is progressively decreased as the trunk is raised toward the vertical, in the sitting (fig. 1 *B*) and standing positions (fig. 1, *C* and *D*). In the extended standing position, this inclination to the right tends to be further neutralized by the increased forward thrust of all the viscera (following the increased sacrolumbothoracic anterior convexity which is due to the extension, adduction and inward rotation of the lower extremities), and also by the visceral pull being directed more and more downward and forward as the direction of gravity becomes more and more cephalocaudad; the increased forward thrust now makes all the viscera still more responsive to gravity and they tend more and more to fall downward, forward and mediad (fig. 1 *D*).

The sagging to the right (right lateral version) seems to be determined by the weight of the larger right lobe, and it seems to be more or less operative in all relaxed positions and to be conveyed to the left lobe till checked by the falciform ligament. Aside from this sagging to the right, the first step in ptosis of the liver due to insufficiently antagonized gravity is a forward rotation (anteversion), and when the abdomen is opened its degree is plainly marked by the appearance of the whitish, sodden, peritoneal surface which in the supine position had been in prolonged contact with the domes of the diaphragm. In its descent, the right lobe tends to be retarded by the right kidney and by the right half of the transverse colon and to come to rest with its lower edge on the small intestine (especially if the latter is distended), the hepatic flexure, the sustentaculum hepatis when present, and, perhaps, the adjacent ascending colon. The left lobe appears to be less firmly attached than the right and more easily displaceable, though following similar paths of anteversion and movement to the right, progress in the latter direction meeting evident limitation at the falciform ligament (fig. 1, *B*, *C* and *D*).

Backward rotation of the liver (retroversion) occurs whenever the posterior portion of the organ is depressed from above or whenever the anterior portion is elevated from below. It is one of the changes which may occur in the second, or diaphragmatic, type, of ptosis en masse,[1] and it may occur temporarily, at any time, as the result of excessive distention of the intestines or stomach. In experiments here made, it has been the only factor found capable of lowering the first portion of the duodenum and its connection with the antrum, so as to produce the so-called tubular type of stomach (fig. 4 *F*).

Ptosis of the liver (especially the forward movements of rotation and descent) is antagonized directly by competence of the upper part of the abdomen, but if the lower part of the abdomen is incompetent, the downward movement may continue with its resulting traction

(gravity type of ptosis en masse [1]). On the other hand, if the lower part of the abdomen is competent and the upper part, incompetent, the downward movement tends to be modified and the forward movement emphasized, with resultant modification of traction (on the diaphragm, the thoracic viscera and the wall of the body) and pressure, the forward movement making toward epigastric projection and expansion of the subcostal angle (diaphragmatic type of ptosis en masse [1]).

When the liver is lifted, upward traction is made on all the abdominal viscera, and in a contrary sense, all the abdominal viscera thus have a potential capacity for traction on the liver. The most fixed portion of the liver is posteriorly where the inferior vena cava is attached to it, and just below the point at which this large vessel penetrates the diaphragm to enter the right auricle. Hence, this is the ultimate point of resistance in ptosis of either type which affects the liver.

Lungs.—In ptosis of the lungs, these organs descend by elongation or other changes in shape, as the thorax shares in the changes in body form and in the action of the diaphragm due to ptosis en masse.

Always filling the closed pleural cavities in which they lie free, the lungs expand in all directions from their anchorage at their hili, according as the enlarging movements of their limiting parietal boundaries permit, these boundaries being the thoracic cage and the diaphragm (fig. 3 *C*).

Hence, the descent, retraction, flattening, elongation and changed action of the boundaries which have been demonstrated as the result of the first or gravity type of ptosis en masse mean the descent, retraction, flattening, elongation and changed action of the lungs (fig. 3, compare *D* with *E*; compare with fig. 3, *b*, in a preceding paper [1]). Similarly, the descent, flattening, broadening, shallowing and forward projection of the diaphragm, the increased anteroposterior diameter of the thoracic cage, with increasing downward and forward obliquity of its axis, and the changed action of these boundaries, which have been demonstrated as the result of the second, or diaphragmatic, type of ptosis en masse, mean corresponding changes in the position, shape and action of the lungs (Vietor,[1] fig. 4, *c*).

These changes in the surroundings of the lungs explain why their ptosis may not be confirmed by percussion of the parietes, since, as these organs descend, the enclosing parietes also descend. In this study, the left lung and the left dome of the diaphragm appear to descend more readily than the right, this change seeming to be related to the more ready descent of the left lobe of the liver (fig. 1, compare the thorax in *B*, *C* and *D* with that in *A*).

Heart.—In ptosis of the heart, this organ tends to rotate downward and from left to right toward the median line, the apex leading and the portion to the right of the median line also moving mediad.

Lying free in the closed and fixed pericardium, the heart has its anchorage in what might almost be called its hilus, which consists of its continuing afferent and efferent vessels and nerves. The pericardium is broadly attached to the central tendon of the diaphragm and is continued upward for a short distance on the large vessels at the base of the heart, being continuous also with the hili of the lungs, and with the upward continuing structures of the mediastinum and its other viscera. The central tendon of the diaphragm is the highest portion of this muscle, and it gives the impression of being held up by the mediastinal tissues even when the lateral domes fall lax and descend (fig. 3, *D* and *E*). Both the central tendon and the mediastinal tissues are very firm in their consistency, and they stretch or fall only under the influence of great stress, showing comparatively slight change even when the lungs and heart show profound changes. This degree of stress seems to develop as the thorax retracts, narrows and elongates in ptosis en masse.

The left dome of the diaphragm is lower than the right, and it also tends to descend more easily, and under the stress of ptosis en masse the left side of the heart, which is also the freer portion, tends to follow it, the apex leading (fig. 3 *D*). As the ptosis progresses, the heart rotates, as it were, from left to right and from above downward, on its fixed mediastinal base, appearing more and more elongated and narrowed, and suggesting a tubular shape. At the same time, the heart to the right of the median line similarly retracts, but a little from right to left, toward the attached base (fig. 3, compare *D* with *E*). The heart also tends to fall backward, the retracted and narrowed chest walls, which narrow the posterior planes as well as the anterior ones, tending to antagonize and make more difficult not only the backward expansion of the lungs, but also the mediad expansion of the posterior margins, the latter expansion normally pushing and holding the heart forward in the chest, as especially shown on the right side in fig. 3 *E*.

The degree of traction and stress exerted progressively through these changes on the cavities of the heart and on its afferent and efferent vessels is evident. Less evident, but just as definitely to be traced, are the traction and stress on the hili of the lungs and on all the connected and related viscera and tissues which extend upward, that on the thymus and its connections showing particularly clearly in fig. 3 *D*.

SUMMARY

1. The fundamental step in splanchnoptosis is incompetence of the abdominal walls, due to failure in the development or coordination of the complex reflexes through which the muscles of these walls support the viscera by antagonizing gravity, overdescent of the diaphragm and persistence of the vestigial binding of the extremities to the trunk.

2. The next step is forward projection of the viscera and shallowing of the paravertebral fossae. This forward projection of the viscera marks the preparatory stage of splanchnoptosis. The next step is the essential stage of descent of the viscera and of traction on their intervisceral and parietal attachments, on their nerves and blood and lymph vessels, and on the related body walls. All changes in position of the viscera cause corresponding changes in the body form.

3. The viscera may be displaced en masse, or individually or in varying combinations. No organ or structure is exempt, but the most easily displaceable individual viscera are the kidneys, the stomach, the redundant portions of the colon, the liver, the lungs and the heart.

4. When the kidneys and suprarenals are projected forward, they enter on the lumbo-iliac inclined planes which furnish direct and inviting paths for descent. As the kidneys descend, they separate from the suprarenal glands, the intervisceral attachments elongating and making traction on the suprarenal glands which, themselves, elongate but remain fixed. Traction is also made on all the structures of the hili.

5. The distending stomach normally finds a descending oblique plane which guides it downward, forward and to the right, though its fundus remains under the left vault of the diaphragm. Ptosis occurs to a greater or less extent along the same path, but continuing descent causes elongation of the body of the stomach, the lower part of this portion descending below the antrum which remains high, thus developing the characteristic pipe bowl shape.

6. The movable part of the first portion of the duodenum tends to share in the movements of the antrum, and it may undergo traction, pressure, kinking, torsion or obstruction.

7. The spleen tends to descend with the stomach and to elongate, its lowest portion becoming tongue-shaped and extending downward and forward on the splenic flexure.

8. The transverse colon is always more or less redundant, forming one or more loops. When the loops are unfolded, they tend to descend, to exert traction on their attachments and to cause kinking and stasis at their angles. Even a moderate descent may cause traction on the stomach, the first portion of the duodenum and the neck of the gallbladder.

9. The liver remains under the right vault of the diaphragm, but, within the limits of its attachments, it is subject to forward, backward and lateral rotations. When the traction on its attachments exceeds its limitations, its tissues yield, and it becomes wholly or partially elongated or otherwise modified in shape.

10. The lungs always remain attached at their hili but descend by elongation or by other changes in shape, as the thorax shares in the changes in body form and in the altered action of the diaphragm due to ptosis en masse.

11. The heart, through the pericardium and the other firm mediastinal tissues, remains attached to the structures at its base, but it tends to rotate downward, and from left to right, toward the median line, the apex leading, and the portion to the right of the median line also moving mediad.

INFLUENCE OF CONGESTION ON TUBERCULOSIS

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About ninety years ago Rokitansky[1] observed a marked inconspicuousness of pulmonary tuberculosis in passively congested lungs. He asserted that diseases of the heart and of the blood vessels producing passive congestion of the lungs are a preventive of phthisis. How these observations led Bier to introduce as a therapeutic measure the artificially produced passive hyperemia that now bears his name is a matter of history.

Since the reports of Rokitansky, many able clinicians have been impressed by the favorable influence on tuberculosis of cardiac or pulmonary diseases which invoke passive congestion. They likewise have been impressed by the unfavorable influence of diseases which are associated with hyperventilation of the lungs. Among those who have made definite comment on these phenomena are Osler, Weiss,[2] Walsh,[3] Fishberg,[4] Hoffmann,[5] Brügelmann and Sewall.[6] Certain pathologic states, such as mitral stenosis and cardiac decompensation, are definitely associated with chronic passive congestion of the lungs. Weiss expressed the opinion that in mitral stenosis pulmonary tuberculosis is infrequent as a result of the venous congestion. Fagge's postmortem record shows 4 cases in thirty years, and according to Kidd's statistics the incidence of mitral stenosis in tuberculosis is 1 in 500. Walsh observed that cardiac decompensation and active tuberculosis do not develop concurrently.

Certain pathologic states, such as pulmonary stenosis and hyperthyroidism, are provocative of a situation in the lungs which is the opposite of congestion—that is, hyperventilation. Osler stated that

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all forms of congenital heart disease, particularly pulmonary stenosis, predispose to tuberculosis. It has been observed that tuberculosis has a very unfavorable course in exophthalmic goiter.

Rokitansky thought that pulmonary emphysema and tuberculosis maintain a relationship of mutual exclusion, and Brügelmann felt that a person with asthma is immune to tuberculosis. Reports of cases have been made in more recent times, however, which lessen the strength of these two opinions. Malone,[7] though stating that bronchial asthma coexisting with tuberculosis is relatively infrequent, reported: that in 157 cases of bronchial asthma, 18 per cent of the patients had tuberculosis as shown by roentgen examination, though there was no mention of the activity of the lesion (Manges and Hawley); that in 20 cases of asthma with tuberculosis, the sputum gave positive reactions in 10 (Pollak), and that in 189 cases of asthma, 3 per cent of the patients showed tuberculosis (Unger). There is some dispute, however, as to whether pulmonary emphysema and bronchial asthma are always productive of or associated with passive congestion of the lungs.

In tuberculosis of tissues other than the lungs, Bier's congestive hyperemia is believed to be beneficial. Its use, particularly in tuberculosis of the joints, skin, bones and thecae of the hand, is advocated in modern textbooks on surgery. Laënnec felt that tubercles and cyanosis are antagonistic. Though great benefit and sometimes a cure have been attributed to the congestion, no adequate explanation has been made for the phenomenon.[8]

Thus an experimental problem presents itself concerning the influence that chronic passive congestion may exert on the initiation and progress of tuberculosis. Since the favorable influence which has been observed clinically has been attributed to increased carbon dioxide concentration, it is within the province of such an investigation to determine the effect of varying concentrations of the commoner atmospheric gases on the tubercle bacillus in vitro.

We have been able to find only two references to animal experimentation on this subject, that of Levinson and Peterson and that of Corper and Goldberg, to which we shall refer in the report of our work with guinea-pigs.

Though ligation of the pulmonary artery has been done in human beings as well as in experimental animals,[9] no one, to our knowledge,

7. Malone, J. T.: Bronchial Asthma and Tuberculosis, U. S. Vet. Bur. M. Bull. **4**:222 (March) 1928.

8. Da Costa, J. C.: Modern Surgery, General and Operative, ed. 8, Philadelphia, W. B. Saunders Company, 1919, p. 260.

9. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925, vol. 2, p. 484. Bruns: Beitr. z. Klin. d. Tuberk. **24**:253, 1913.

has tried ligation of veins as a therapeutic or experimental measure. Arterial ligation is reported to have little or no influence on tuberculosis.[10]

We feel that information on this problem not only is important in connection with a possible application in the surgical treatment of pulmonary tuberculosis but is pertinent to a consideration of the favorable factors attending pulmonary collapse.

CULTURE OF THE TUBERCLE BACILLUS IN VITRO WHEN SUBJECTED TO VARYING CONCENTRATIONS OF OXYGEN, CARBON DIOXIDE AND NITROGEN

In 1918, Wherry and Ervin[11] observed and performed several experiments to show that the growth of a culture of the tubercle bacillus was completely inhibited when carbon dioxide was absent. The carbon dioxide was removed by sodium hydroxide to which the culture tube was connected. They observed that concomitant with the growth of the organism the supply of oxygen in the culture tube was depleted, but there was usually enough oxygen in a small closed test tube to yield a confluent layer of growth. During the growth, carbon dioxide was elaborated. When they subjected a culture to 13 per cent carbon dioxide in one tube, no growth was obtained.

In 1921, Corper, Gauss and Rensch,[12] considering these findings significant, extended the studies. They observed that 3 per cent carbon dioxide caused some inhibition of the growth of tubercle bacilli and that 15 per cent was tuberculocidal. They confirmed the fact that the bacillus fails to start initial growth in an atmosphere free from carbon dioxide. Cultures of tubercle bacilli were buried in the tissues of living animals and so arranged that the author felt that the gases in the tube would come into equilibrium with those in the tissues. The latter were controlled by buried tubes to which atmospheric air was allowed ingress. The completely buried cultures were inhibited as compared to the controls. They found that in a closed tube after the carbon dioxide elaborated by the growing bacillus reached a concentration of 5.5 per cent growth was inhibited. On the basis of these results they felt that the concentration of carbon dioxide normally existing in the human body is sufficient to inhibit definitely the growth of tubercle bacilli and that this factor is extremely significant in resistance to the disease.

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10. Van Allen, C. M.; Nocoll, G. L., and Tuttle, William: Lung Changes After Occlusion of Pulmonary Artery Branches by Embolus and by Ligature, Yale J. Biol. & Med. **2**:363 (May) 1930.

11. Wherry, W. B., and Ervin, D. M.: The Necessity of Carbon Dioxide for the Growth of B. Tuberculosis, J. Infect. Dis. **22**:194, 1918.

12. Corper, H. J.; Gauss, Harry, and Rensch, O. B.: Resistance to Tuberculosis: A Non-Immunologic Chemical Factor Worthy of Consideration, J. A. M. A. **76**:1216 (April 30) 1921.

In 1925, Novy, Roehm, Soule and Novy, Jr.,[13] carried out detailed and elaborate experiments in the study of microbic respiration with a direct application to the tubercle bacillus. A known strain of human Bacillus tuberculosis was used. The culture medium was an agar base with glycerin, dextrose or serum.

Some of the results obtained were as follows:

1. From 100 to 150 cc. of oxygen (or its equivalent, from 500 to 700 cc. of air under normal cultural conditions) must be provided in order to obtain a rich growth. The yield of carbon dioxide was slightly less than the amount of oxygen consumed, as much as 150 cc. of carbon dioxide being produced by a single culture. When the bacilli were grown on glycerin agar, the respiratory quotient (corrected) was 0.836.

2. In an ordinary closed culture tube the oxygen was removed in a few days by the inoculum, and no visible growth resulted. (Therefore in an effectively sealed tube absence of growth or slow growth means an insufficient supply of oxygen.) When all of the oxygen (20.9 per cent) was consumed by the culture the carbon dioxide yield reached 17.5 per cent. Thus, as the respiratory quotient was less than 1 and some carbon dioxide was dissolved in the medium, considerable negative pressure was developed.

3. Growth occurred with any oxygen concentration, the optimal value being from 40 to 50 per cent. With a concentration of 100 per cent, growth developed as isolated, thick, moist, white colonies which at the end of fifty-eight days were infective. At a very low oxygen tension the growth was retarded but continued until "the last atom of oxygen was consumed."

4. In atmospheres containing from 10 to 50 per cent of carbon dioxide growth was not inhibited. When the concentration of carbon dioxide was 60 per cent or more, there was some inhibition, but fair growth was obtained in 90 per cent carbon dioxide. A culture which developed in from 85 to 96 per cent carbon dioxide for fifty-nine days was viable and infective.

5. Continued removal of carbon dioxide from the culture tube by alkali did not stop growth. The experimenters felt that any inhibition under such conditions was due to desiccation by the alkali, since moisture is an important factor in securing rich and even growths.

On the basis of these results, the conclusion was drawn that the slow multiplication of the tubercle bacillus in the body is explainable from the standpoint of growth in the presence of diminished oxygen tension. An indefinite supply of oxygen under a tension corresponding to a few millimeters of mercury will probably enable the organism to

13. Novy, F. G.; Roehm, H. R.; Soule, M. H., and Novy, F. G., Jr.: J. Infect. Dis. **36**:109 and 343, 1925.

grow, though very slowly. Rest and a rich diet in checking the progress of the disease probably act by reducing to a minimum the available oxygen supply in the tissues.

Up to this time the results of these two investigations had stimulated authors to place emphasis on entirely different phenomena with regard to the influence of atmospheric gases on the tubercle bacillus. Corper emphasized the inhibiting influence of carbon dioxide while Novy emphasized the inhibiting influence of an atmosphere poor in oxygen.

In 1927, Corper and his co-workers [14] observed that in their experimental animals the lungs were involved to a greater extent after the intravenous administration of tubercle bacilli than were other organs, particularly the liver. In attempting to find an explanation for this on the basis of gaseous tension, he repeated and modified his former in vitro work. The sealed test tube method was abandoned, and the gas mixtures were arranged to flow constantly over the cultures from large feed tanks. By this method Corper observed no inhibitory effect of carbon dioxide on the cultures until a concentration of 54.5 per cent was reached. On the contrary, concentrations of carbon dioxide greater than that in air and as high as 14 per cent seemed to have a stimulating effect on growth. Oxygen was again found necessary for growth, and cultures were inhibited in very low concentrations. No growth was obtained in 0.1 per cent oxygen in six weeks. Cultures were then submitted to atmospheres the gaseous composition of which was that of alveolar air and that of mixed venous blood. The figures for mixed venous blood were taken from L. J. Henderson and were: carbon dioxide, 47 mm. tension (7.48 per cent), and oxygen, 35 mm. tension (5.57 per cent). For alveolar air they were: carbon dioxide, 40 mm. tension (6.37 per cent), and oxygen, 100 mm. tension (15.94 per cent). The tubercle bacilli grew better in the atmosphere of alveolar air than in the gases of mixed venous blood, and thus Corper felt it fair to assume that they should grow more rapidly in the lungs than in the spleen, kidneys and bone marrow and in all these organs more rapidly than in the liver.

He stated further that conditions which can change the oxygen tension in tuberculous foci from 0.7 to 3.8 mm. may be sufficient to change a quiescent focus into progressive disease. One of the most important single factors influencing the oxygen tension is the hydrogen ion concentration of the blood by its effect on the dissociation of oxyhemoglobin. Fatigue and starvation cause an increase, while rest and nourishment cause a decrease, in available oxygen in this way.

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14. Corper, H. J.; Lurie, M. B., and Uyei, Nao: The Variability of Localization of Tuberculosis in the Organs of Different Animals: III. The Importance of the Growth of Tubercle Bacilli as Determined by Gaseous Tension, Am. Rev. Tuberc. **15**:65, 1927.

At first we were led to believe that the inhibition of our cultures in sealed tubes was due to high concentrations of carbon dioxide, but further experiments proved conclusively that this was not the case. Our results bear out the conclusions that oxygen must be available or the growth will cease and that concentrations of carbon dioxide as high as 38 per cent will not materially inhibit the growth. A small amount of carbon dioxide is necessary for initial growth to take place.

The virulent Gluckson strain of B. tuberculosis was used in the in vitro and in part of the animal experiments.[15] We used Corper's gentian violet-glycerin-potato medium for all in vitro experiments and subcultures.

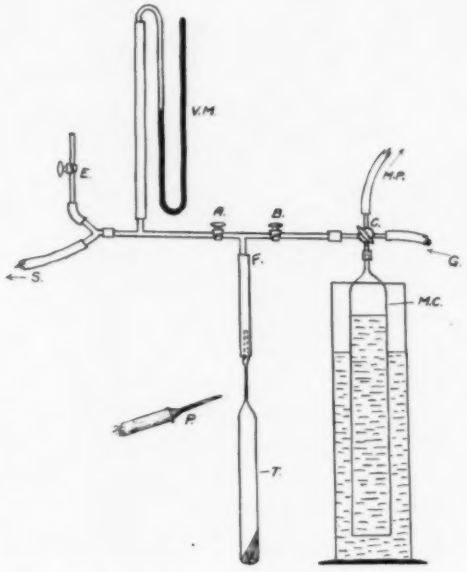

Fig. 1.—By manipulating the threeway stopcock (*C.*), mercury is drawn up to the capillary mark in the neck of the graduated mixing cylinder (*M.C.*) by means of the mouthpiece (*M.P.*). The desired gases are then allowed to flow in through *G.*, the mercury levels in the chamber and the reservoir being kept equal while readings are taken. With stopcocks *E.* and *C.* closed and *A.* and *B.* open, the gas in the culture tube (*T.*) is sucked through *S.* until a near vacuum is produced. This is indicated when the vacuum manometer (*V.M.*) presents equal mercury levels. (A water suction pump will fail to produce a complete vacuum by at least the vapor tension of water, but for our purpose this was negligible.) With *A.* closed and *B.* and *C.* open, *T.* is filled with the mixture. The gas in *T.* is again sucked out, and after two or three such washings the tube is finally filled with the mixture under atmospheric pressure and the capillary neck quickly sealed with a hot pencil flame (*P.*).

15. The Gluckson strain of B. tuberculosis was supplied to us by H. J. Corper.

EXPERIMENTS

After inoculation of the potato medium contained in 1 by 10 inch test tubes, the necks of the tubes were pulled out so that they fitted

TABLE 1.—*Results of Experiments A, B and C*

Experiment A

Date of inoculation: 10/12/31 Date of sealing: 10/12/31 Tubes opened: 12/7/31

Nitrogen, per Cent	Carbon Dioxide, per Cent	Growth After 56 Days*	Comment
99	1	0	After six weeks, the tips of the tubes were broken, and the cultures were incubated for another six weeks in free communication with air; the medium became too dried out to be of any value though growth had developed in the tubes containing 7 and 15 per cent carbon dioxide
98	2	0	
97	3	0	
96	4	0	
95	5	0	
93	7	0	
85	15	0	
70	30	0	
50	50	0	
100	0	0	
Control.....		++++	

Experiment B

Date of inoculation: 10/12/31 Date of sealing: 10/12/31 Tubes opened: 12/7/31

Oxygen, per Cent	Nitrogen, per Cent	Growth After 56 Days	Growth After Communication with Air (6 Weeks)
2	98	0	?
5	95	Trace	+++
10	90	0	++
50	50	0	?
75	25	0	?
95	5	0	?
100	0	0	?

Control: Medium became too dried out to be of any value

Experiment C

Date of inoculation: 9/11/31
Date of sealing: 9/11/31
Tips of tubes broken and cotton stoppers inserted: 11/10/31 (60 days)

Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 60 Days	Growth After Communication with Air (6 Weeks)
0	100	0	0
50	50	+	+++
70	30	++	+++
80	20	+	+++
85	15	0	++++
90	10	0	++++
95	5	++	+++
96	4	++	++
96	4	+++	++++
97	3	+++	+++
97	3	++	+++
98	2	+++	++++
98	2	++	+++
99	1	0	+++
99	1	+	+++
100	0	0	++++
Air	..	++	+++
Control	..	++++	

* In all the tables the amount of growth is represented in the customary manner as being from + to ++++, the latter being maximum.

tightly in a piece of ordinary suction tubing. An apparatus (fig. 1) was designed for the evacuation of the tubes. They were subsequently filled with the desired gases from the mixing chamber and then sealed with a pencil flame blow torch. The cultures were incubated at 37.5 C.

for at least six weeks. (A definite error must be admitted in the mixing of the gases, but this did not prove to be of relative importance under the circumstances of the experiment.)

The results of experiments A, B and C are shown in table 1. The best growth was obtained in from 2 to 5 per cent carbon dioxide. After subsequent exposure to air for six weeks, only the tube containing 100 per cent carbon dioxide failed to show growth. In all of the tubes except the one containing air the bacilli grew in isolated, large, umbilicated colonies. Sometimes abundant growth occurred in the fluid at

Fig. 2.—Photographs of cultures in high oxygen tensions, showing the character of growth in large, isolated, crater-like colonies. The abundant growth in the fluid at the bottom may be seen in the tube containing 97 per cent oxygen and 3 per cent carbon dioxide.

the bottom of the tubes (fig. 2). Novy obtained the same result in high concentrations of oxygen and since such a characteristic growth does not occur in any concentration of carbon dioxide when the oxygen tension is low, we feel that it can be attributed to high oxygen tension.

Experiments D and E (table 2) indicate an unexplained irregularity in results when the gas mixtures are imposed on cultures which have already attained an initial growth. The only explanation that we can offer for this is that organisms which have already attained a growth cannot adapt themselves to sudden marked changes in gaseous tension.

When the tips of the tubes were broken, our attention was called to the negative pressure which had developed in some of the tubes. We then measured the negative pressures and found that they ranged to as low as —72 mm. of mercury and were lowest for the cultures

TABLE 2.—*Results of Experiments D and E*

Experiment D

Date of inoculation: 10/12/31

During the two weeks before sealing, all of the cultures presented a fine granular growth evenly distributed over the surface of the potato medium

Date of sealing: 10/26/31

Oxygen, per Cent	Carbon Dioxide, per Cent	Nitrogen, per Cent	Growth After 53 Days*
75	0	25	#
65	0	35	#
23	1	76	+
22	2	76	+++
20	4	76	#
18	6	76	#
16	8	76	#
14	10	76	#
Control, evacuated, filled with air and sealed			+++
5 controls, unsealed			++++

Experiment E

Two series of cultures were used. In one series growth was allowed to develop for eighteen days before sealing, in the other, the tubes were sealed on the day of inoculation. All tubes were sealed at the same time so that the same gas mixture could be used in corresponding tubes

	Series A	Series B
Date of inoculation	1/30/32	2/17/32
Sealed	2/17/32	2/17/32

Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 6 Weeks*	Growth After 6 Weeks
100	0	+++	0
0	100	#	0
99	1	+++	+++
96	4	#	++++
95	5	++	++
94	6	Ceased growing	++
92	8	++	++
90	10	+++	+++
85	15	+++	++
80	20	+++	0
70	30	+++	0
50	50	#	0
25	75	#	0
Air		+++	+++
Control		++++	++++

* # indicates that the growth turned black and the bacilli had a granular appearance microscopically and failed to grow on subculture. The medium was not decolorized as it was by mature cultures. + indicates that growth continued, decolorizing the mediums, and yielded active growth after transplantation.

showing the most abundant growth. There was relatively little negative pressure in the tubes showing no growth. (No corrections were made for temperature, but the negative tensions were out of all proportion to the small differences of temperature at which we worked.) We therefore concluded that the capacity of even a 1 by 10 inch test tube was much too small to warrant any conclusive interpretation except in tubes which did not present even an initial growth.

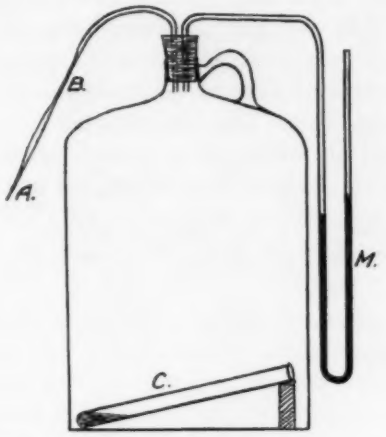

Fig. 3.—A gallon jar fitted with a mercury manometer (*M.*) and a sampling tube drawn out in two places (*A.* and *B.*). The Haldane sampling bottle is fitted by mercury-filled rubber tubing to *A.* By breaking *A.* within the tube, the sample could be taken, after which the sampling tube was sealed at *B.* Paraffined rubber stoppers proved to be an effective seal for these bottles. At the conclusion of the experiment another sample was taken in a similar manner at *B.*

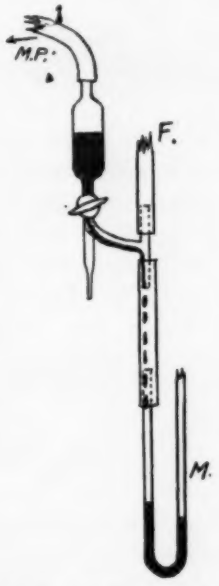

Fig. 4.—Method of sealing gallon jars with a mercury manometer (*M.*). The piece is attached (*F.* to *F.*) to the original apparatus.

We then planted small cultures in sealed gallon bottles (fig. 3). The bottles were fitted with mercury manometers and glass tubes from which samples of the gas could be drawn for analysis at the beginning and at the end of the experiment. The bottles were evacuated through the manometer tube, filled with the desired gas from the mixing chamber and sealed by dropping mercury into the manometer. To accomplish this the apparatus shown in figure 1 was modified by adding the piece shown in figure 4 and by supplying a 2 gallon mixing chamber using water as a displacement fluid. The results of this experiment are shown in table 3.

As an added experiment to show whether retarded growth in sealed tubes was due to accumulated carbon dioxide or to lack of oxygen, we devised the apparatus shown in figure 5. The bottle was filled with pure oxygen at a tension about 20 mm. greater than atmospheric pressure. Cultures were planted and sealed on each end of the T tubes (the culture tubes initially containing air) so that from time to time, by giving the stopcocks a turn, an adequate supply of oxygen was assured. We assumed that under these circumstances the accumulated carbon dioxide would not escape into the bottle. This was verified by analyzing the gas in the bottle for carbon dioxide before and after the experiment. Cultures sealed with paraffined stoppers and open cultures were used as controls.

TABLE 3.—*Results of Experiment F*

Date of inoculation: 1/27/32
Date of sealing: 1/27/32
One culture in a standard bacteriologic test tube was placed in each gallon jar

Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 6 Weeks
100	0	0
95.7	4.3*	+++
62	38*	++++
Air		+++
Control		++++

* Analysis of a sample of gas from a bottle (Haldane apparatus). Gas was withdrawn from the bottles until the manometer columns showed the pressure in the bottles to be higher by 20 mm. of mercury than atmospheric pressure. There was no appreciable change from this reading in any of the bottles throughout the six weeks, eliminating the possibility of leakage.

The growth in the experimental tubes and in the open tubes after six weeks was equal in amount and was designated by $+++$, while that in the paraffined tubes was less in amount, being about $++$.

In the course of the experiments we were greatly impressed by the aerobiosis of the tubercle bacillus. This has been commented on by others, but we feel that it is deserving of considerable emphasis. Particularly is this true for those who are using the cultural method as a diagnostic procedure. The capacity of the ordinary bacteriologic test tube is small, and the content being air, only a small amount of oxygen will be available. While not always successful, an attempt is usually

made to seal such tubes completely in order to prevent the medium from drying out. In some tubes the sealing will be complete, and if so the cultural conditions will be far from the best obtainable. We have found the following alternative method simple and satisfactory: A beaker or other receptacle is placed in a large-mouthed jar con-

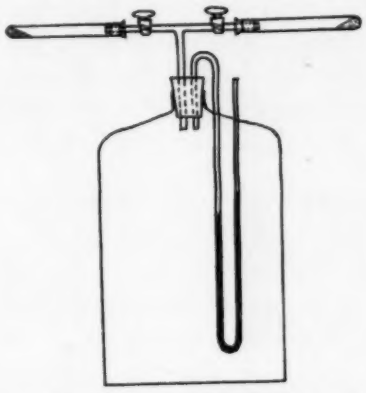

Fig. 5.—A gallon jar containing 100 per cent oxygen under slightly greater than atmospheric tension. By a single turn of the stopcocks every one or two days, any reduced tension (depleted oxygen) in the culture tubes was replaced with oxygen.

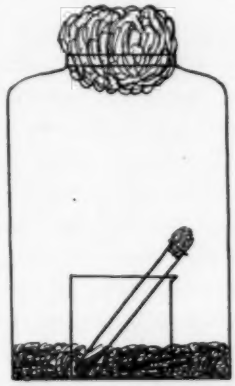

Fig. 6.—A large-mouthed jar with a cotton plug and cotton in the bottom kept saturated with water. Culture tubes kept in such a jar may have free communication with air without danger of the medium becoming dry.

taining some cotton well saturated with water (fig. 6). A large cotton stopper is used to plug the bottle. Under these conditions, cultures on potato or glycerin agar when kept in the beaker need be stoppered only with cotton. Many of our cultures were left open. An adequate supply of oxygen is thus assured, and the medium has no tendency to dry out as long as the cotton in the jar is moist.

CONCLUSIONS

1. In vitro experiments show conclusively that carbon dioxide in significant concentrations does not inhibit the growth of the human tubercle bacillus. On the contrary, a small amount is necessary for the beginning of growth. Concentrations such as are found in alveolar air or in venous blood seem to have a stimulating effect.

2. The tubercle bacillus will not grow in the absence of oxygen. Cultures grow considerably better when allowed free communication with air than when air-containing tubes are sealed, and a simple and satisfactory method of accomplishing this for the routine or diagnostic culture is suggested.

3. Therefore, so far as in vitro experiments indicate, increased carbon dioxide tension is not responsible for any beneficial effect that may be attributed to congestion.

4. The availability of oxygen is a highly significant factor in the growth of the tubercle bacillus.

INFLUENCE OF CONGESTION ON TUBERCULOSIS OF TISSUES OTHER THAN THE LUNG

Corper and Goldberg [16] reported that by constriction of the ear of a rabbit with a rubber band the carbon dioxide content of the plasma in the congested portion was increased from 10 to 20 and even 50 per cent. Following the intradermal injection of tubercle bacilli, the local development of tubercles was retarded, and ulceration with discharge of the contents occurred earlier than in the noncongested auricle of the same animal. There was no effect on the development of multiple metastatic lesions when bovine bacilli were used or on involvement of regional lymph nodes when human or bovine bacilli were used.

Levinson and Peterson [17] reported that there is no striking difference grossly between the passively congested liver of a rabbit and the liver of a control animal as to quantitative distribution or size of tubercles. Histologically, they found a greater deposit of fibrous tissue around and within the tubercles in the passively congested livers. Passive congestion was induced by injecting 0.5 cc. of liquid petrolatum intravenously twice a week for one month.

We feel that the problem of congestion and tuberculosis is important enough to justify more investigation. We do not feel that a marked degree of congestion was definitely enough demonstrated in Levinson and Peterson's rabbits. It should also be remembered that if the oil introduced into the blood stream plugs the capillary bed it will act as

16. Corper, H. J., and Goldberg, Max: Am. Rev. Tuberc. **8**:567, 1924.

17. Levinson, S. A., and Peterson, W. F.: Effect of Passive Hyperemia of the Liver on Tubercle Formation, J. A. M. A. **81**:723 (Sept. 1) 1923.

a foreign body and may itself be responsible for any variance in the tuberculous histologic picture, such as increased fibrosis. Particularly is this true since passive congestion per se is not productive of fibrous tissue.

For a study of the present problem to be in any way conclusive, two fundamental prerequisites must be satisfied: First, the tuberculosis in the controls must prove to be progressive, and second, the congestion of the organs should be as free as possible from complicating factors. In fulfilling the first postulate, our choice of experimental animals was limited. We made a special effort to apply our studies to the guinea-pig because of its definite and uniform susceptibility to human tubercle bacilli. We also attempted to use the lungs of the dogs, and our results with this animal will be given at a later date.

In fulfilling the second postulate, we produced chronic passive congestion by complete or partial venous ligation.

We would stress the first postulate, namely, that the tuberculous lesion must prove to be progressive in the controls. Much of the experimental work which has been done to test the influence on tuberculosis of possible therapeutic devices, whether biologic, chemical or mechanical, has been done by the intravenous injection of tubercle bacilli, and the appearance of tubercles in the treated tissue has been taken to negative any possible benefit of the therapeutic agent or device. It is known that emboli of tubercle bacilli, whether dead or alive, will produce a tuberculous histologic process wherever they lodge, and the process produced by dead bacilli is indistinguishable from that produced by viable bacilli. Of course, the lesion produced by dead bacilli will heal as soon as the toxins of the organisms have been spent. The lesion produced by living organisms may or may not progress. Therefore, we are not interested in, or rather we do not expect to find, a therapeutic agent which will prevent the appearance of a tuberculous histologic picture in the treated tissue. We are concerned chiefly with ascertaining any inhibiting effect of the agent on the progress of a tuberculous lesion when compared with a suitable control. Possibly this effect may be manifest only in the histologic characteristics rather than in the size of the lesion at any particular time in its development. It is important, therefore, to be acquainted not only with the characteristics of the normally developing lesion but with any criteria by which an inhibiting effect could be determined. In general, susceptibility is expressed by degeneration and caseation, the effects so outstanding in children and very susceptible adults, and resembles so markedly the process in monkeys that it has been referred to as "monkey tuberculosis." [18]

18. Fox, Herbert: Some Observations on the Development of Pulmonary Tuberculosis in Lower Animals as Compared and Contrasted with Similar Lesions in Man, Am. Rev. Tuberc. **17**:435, 1928.

Resistance is manifested by fibrosis and calcification. Theobald Smith[19] classified the evidences of tissue resistance in the following order: (1) giant cells; (2) giant cells with a mantle of epithelioid cells showing a tendency to sclerosis and without necrosis; (3) a more extensive process with caseation and calcification; (4) a group of tubercles due to unhindered bacillary growth, forming a large focus, and (5) a rapid

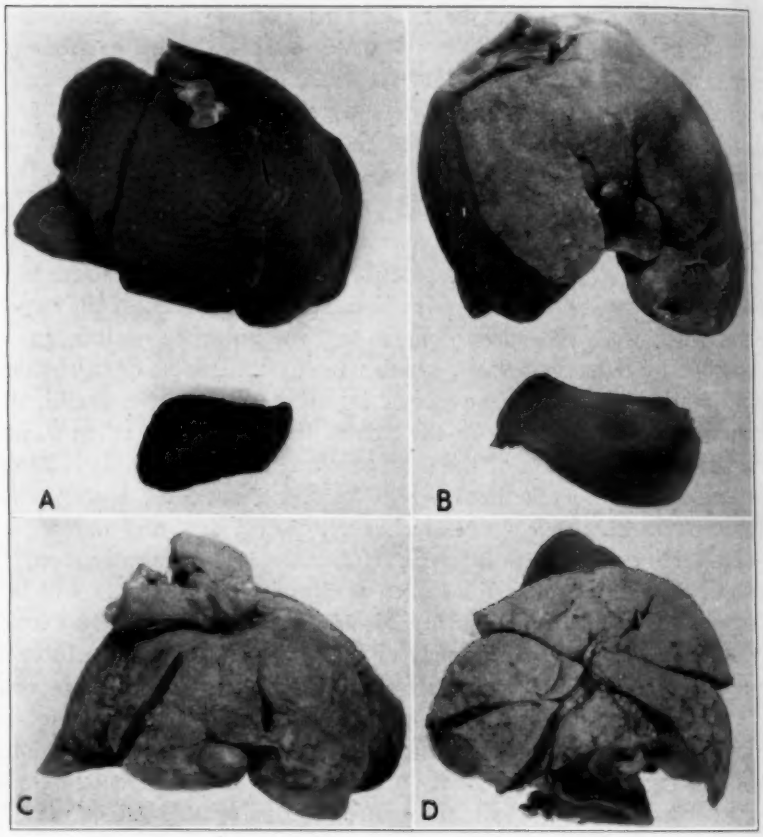

Fig. 7.—*A*, the liver and spleen of a normal guinea-pig (fixed in a dilute solution of formaldehyde, U. S. P. [1:10]). *B*, the liver and spleen of a guinea-pig that died fourteen days after complete ligation of the vena cava (congestion ++). The ligature can be seen beneath the diaphragm. C, the liver of a guinea-pig that died twenty-one days after complete ligation of the vena cava (congestion ++++). Regeneration of the liver is more evident than in *B*. *D*, cross-section of the liver which is shown in *C*, showing the evidence of cell regeneration and fatty degeneration. All the photographs were taken at an equal distance.

19. Smith, Theobald: Certain Aspects of Natural and Acquired Resistance to Tuberculosis and Their Bearing on Preventive Measures, J. A. M. A. **68**:764 (March 10) 1917.

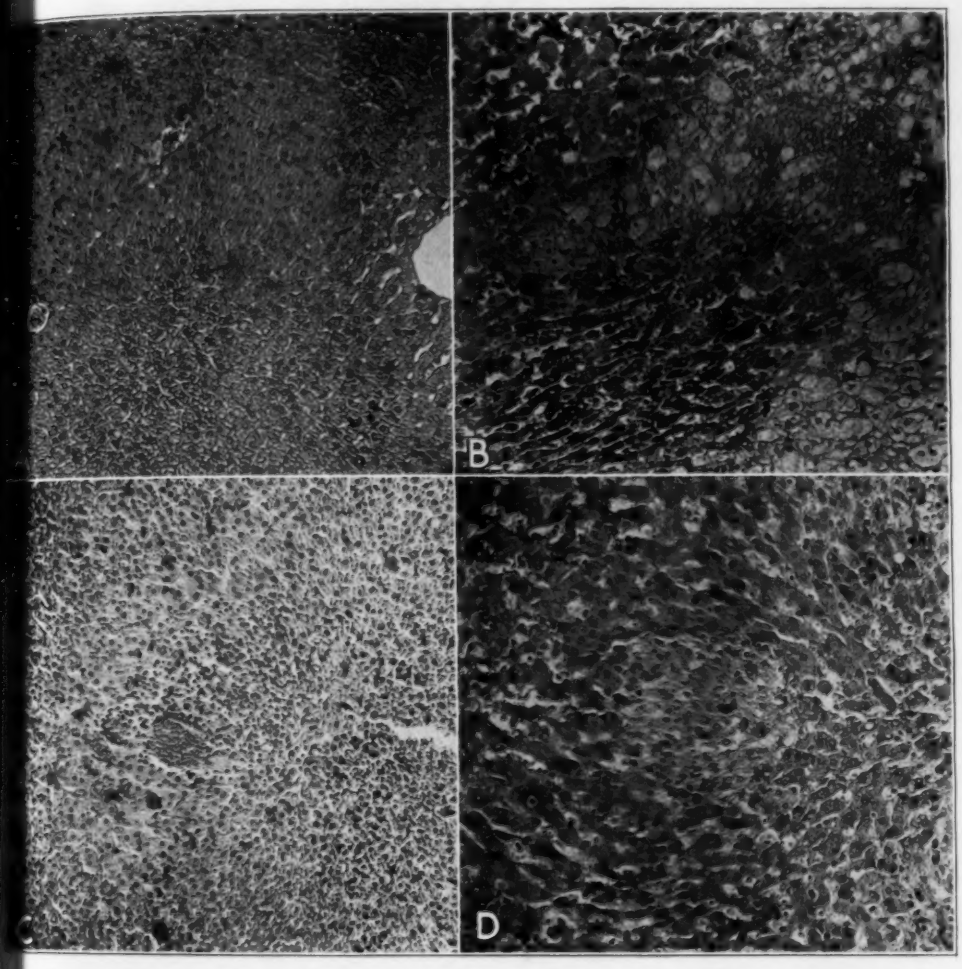

Fig. 8.—*A*, a low power photomicrograph of a section of the liver from a normal guinea-pig. A portal area can be seen on the left, and a central vein on the right. *B*, a section of a congested liver from a guinea-pig that died twenty-three days after complete ligation of the vena cava (congestion ++++). There are marked fatty degeneration and death of cells about the central veins. The viable cells are greatly swollen. *C*, an early tubercle in the liver of a control animal, showing death of the liver cells and the usual infiltration with mononuclear cells. The animal died twenty days after inoculation (tuberculosis +). Giant cells are occasionally seen in such early tubercles. *D*, an early tubercle in a liver congested for thirty days by partial ligation of the vena cava (tuberculosis +; congestion +++). The animal died twenty-four days after inoculation. All the photomicrographs were taken at the same power of magnification.

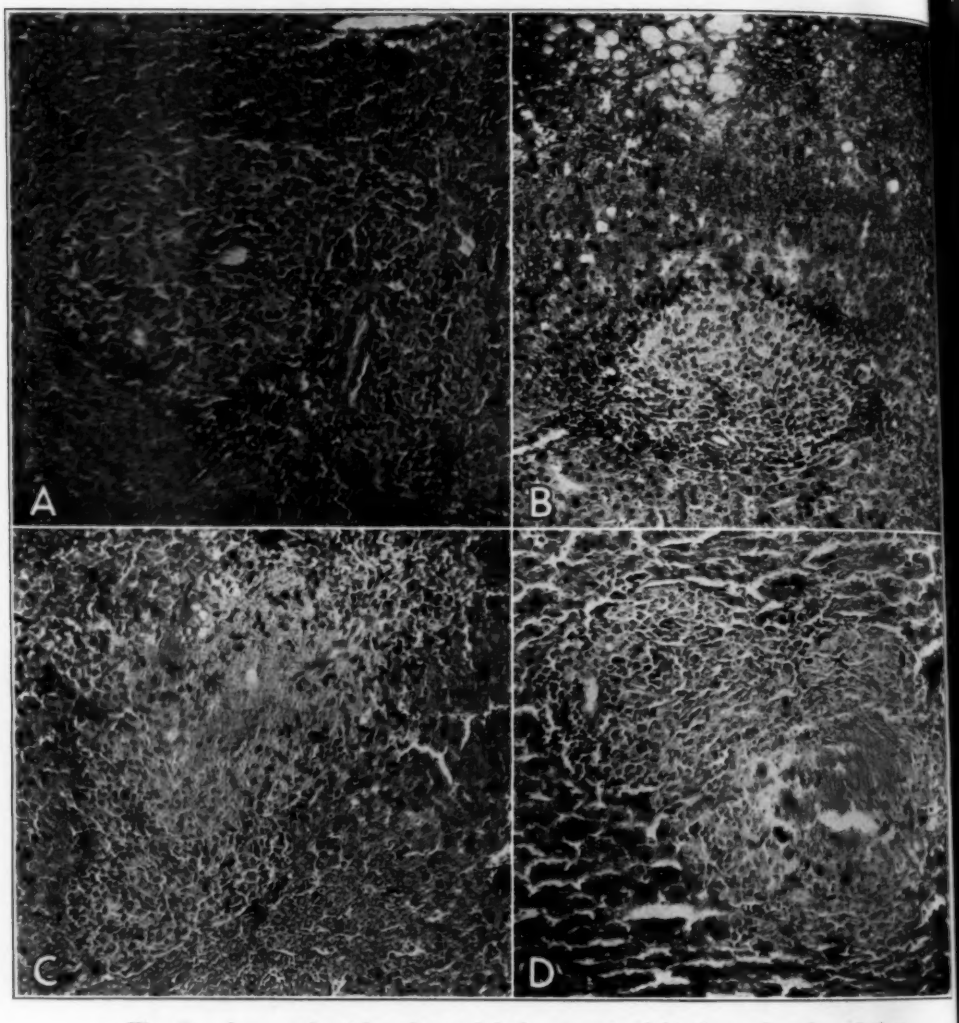

Fig. 9.—*A*, a moderately advanced lesion twenty-eight days after inoculation (tuberculosis +++). The lesion is in a periportal space. *B*, a moderately advanced tubercle twenty-eight days after inoculation in a liver congested for thirty-three days as a result of partial ligation of the vena cava (tuberculosis +++; congestion ++++). The lesion is in a periportal space and shows epithelioid cells. *C*, an advanced lesion in a control animal thirty-three days after inoculation, showing marked caseation (tuberculosis ++++). *D*, an advanced lesion thirty-three days after inoculation in a liver congested for thirty-eight days as a result of partial ligation of the vena cava (tuberculosis ++++; congestion +++).

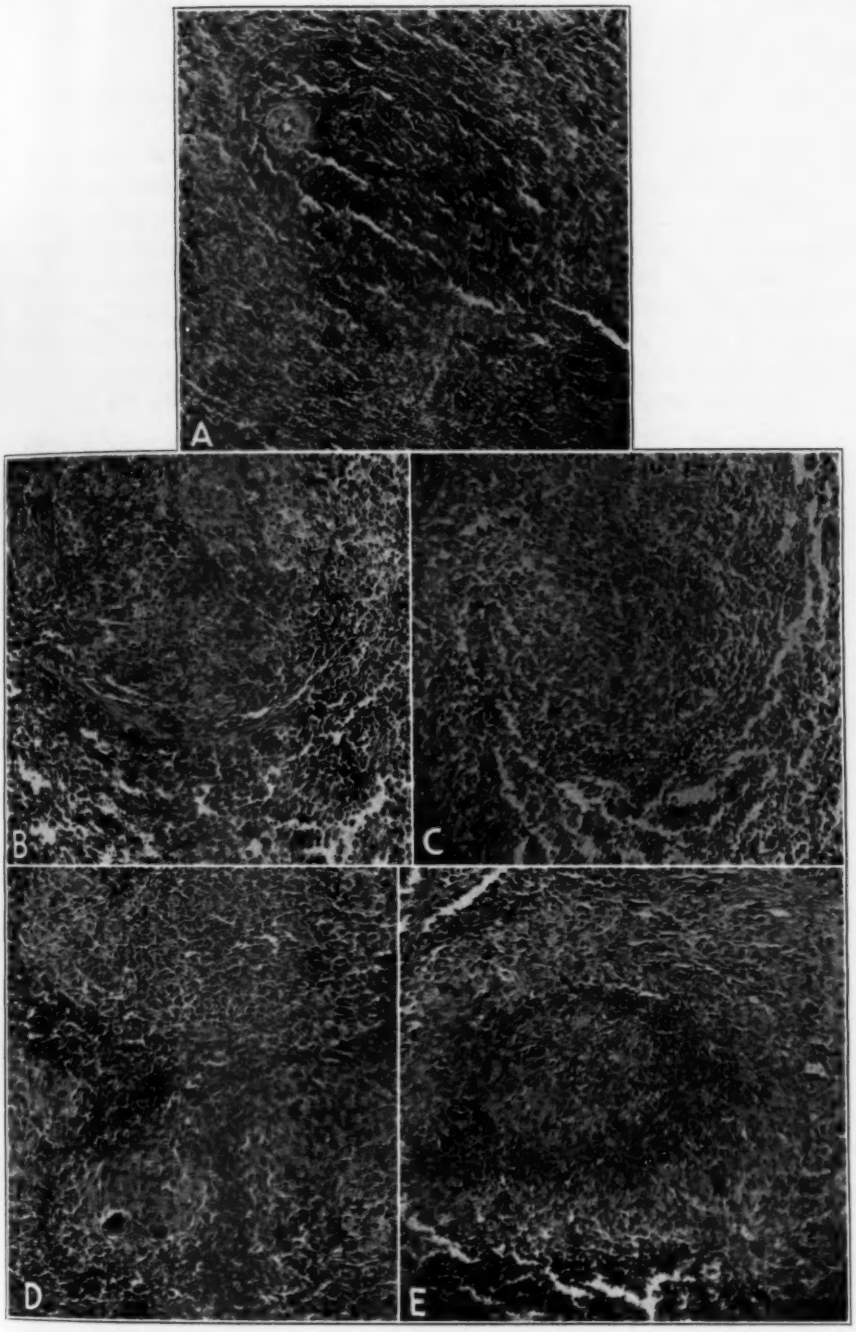

Fig. 10.—*A*, a low power photomicrograph of the spleen of a normal guinea-pig showing a malpighian corpuscle. *B*, a moderately advanced (+++) lesion in the spleen of a control animal twenty-eight days after inoculation. Caseation is present at this stage. *C*, a moderately advanced (+++) lesion twenty-four days after inoculation in a spleen congested for thirty days by partial ligation of the vena cava. *D*, an advanced (++++) lesion in a control animal thirty-three days after inoculation. The tubercles are conglomerate with caseation. Two giant cells are present. *E*, an advanced (++++) lesion twenty-eight days after inoculation in a spleen congested for thirty-three days by partial ligation of the vena cava.

multiplication of the bacilli within a focus with marked necrosis of tissue. It has been shown by Krause [20] that bacilli injected into the groin of a guinea-pig pass by way of the lymphatic system to the superficial and deep inguinal nodes and thence to the lymphatics about the common iliac artery and the abdominal aorta. They empty into the blood stream by way of the thoracic duct at the junction of the internal and the external jugular vein on the left side. The course then is to the lungs and through them to the peripheral organs. The spleen receives organisms entirely from the arterial blood stream, while the liver is supplied by the arterial and the portal stream, the latter coming from the intestinal tract and the spleen. The spleen and the liver are the most frequently and severely involved of the visceral organs, the spleen probably because it is rich in lymphoid tissue and the liver probably because it is fed by the spleen.

COMPLETE LIGATION OF THE INFERIOR VENA CAVA OF THE GUINEA-PIG

By Dr. Hyndman, Dr. Harry Landt, Dr. A. R. Anneberg and Dr. J. D. Goldstein

Under ether anesthesia and with aseptic precautions a midline incision about 1 inch (2.5 cm.) long was made in the abdomen of the guinea-pig, beginning over the xiphoid process. By gently retracting the liver downward and cutting the thin falciform ligament, the portion of the inferior vena cava between the diaphragm and the liver was brought into view. By means of a ligature carrier a ligature of fine black silk was passed around the vein and the vessel was ligated completely. The peritoneum and the muscular layers and then the skin were closed with a continuous black silk suture. The operative mortality, either immediate or within two or three days, was 80 per cent. Five animals, however, lived from twelve to forty-five days, and the wounds were well healed. A few days following the operation the experimental animals and their controls received 2 minims (0.12 cc.) of a diluted suspension of tubercle bacilli (Gluckson strain) in the groin. The suspensions were made fresh each time from young subcultures by shaking with glass beads in sterile physiologic solution of sodium chloride. After we had obtained as fine a suspension as we could by this method the top suspension was diluted until the opalescence disappeared. The effect of complete or partial venous ligation on the liver was marked (fig. 7). Within two weeks the liver became enlarged and presented a marked nodular appearance. Though the engorgement of the spleen was usually evidenced by considerable swelling, this was not constant. The peritoneal cavity at the time of postmortem examination

20. Krause, A. K.: Am. Rev. Tuberc. **4**:135, 1920.

presented a varying amount of ascites, the fluid usually being blood-tinged. The effect on only the liver and spleen was studied. Microscopic sections of these organs were taken and stained with hematoxylin

TABLE 4.—*Results of Experiment G*

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Pathologic Changes		
			Congestion of Liver*	Tuberculosis† Of Liver	Tuberculosis† Of Spleen
1	5	12	+++	0	0
Control	..	15	..	0	0
2	5	16	++++	+	++
Control	..	16	..	0	++
3	4	19	++	+	+
4	4	19	++++	+	+
Control	..	22	..	+	++
5	7	45‡	+++	0	+
Control	..	45‡	..	0	+

* The degree of congestion of the liver is represented by + to ++++, the latter being the maximum. The degree of congestion was determined microscopically, and this agreed closely with the gross appearance of the liver.

† The degree of tuberculosis is designated as follows: 0, no tuberculous histologic changes present in the sections examined; +, only one or two early lesions; ++++, advanced lesions with marked caseation (photomicrographs, figs. 8 to 10).

‡ These two animals were killed after forty-five days and showed marked involvement of the lymph nodes from the inguinal to the peribronchial nodes but no tubercles in the liver.

TABLE 5.—*Results of Experiment H*

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Suspension†	Pathologic Changes*		
				Degree of Congestion of Liver	Tuberculosis Of Liver	Tuberculosis Of Spleen
1	3	19	a	+	0	0
2	0	24	b	+++	0	+
3	6	24	b	+++	+	+
4	3	26	a	+	++	++
5	2	27	c	++++	0	+
6 (control)	..	27	c	..	++	++
7	0	31	a	++++	0	+
8 (control)	..	34	c	..	+	+++
9 (control)	..	34	a	..	+	++
10‡	0	35	a	++	0	0
11‡	0	35	a	+++	0	+
12	6	35	b	++	++	+++
13 (control)	..	38	b	..	++	+++
14 (control)	..	40	b	..	++	++
15‡	5	40	b	++	++	++
16	8	42	b	++++	++	++
17 (control)	..	43	b	..	+++	+++
18 (control)	..	43	b	..	+++	++++
19‡	5	44	b	++++	+++	+++
20	10	55	c	++++	+++	+++
21 (control)	..	55	c	..	+	++++

* The degree of congestion and of tuberculosis is indicated as in table 4.

† Three different suspensions (a, b and c) were used in this experiment and made fresh for each group inoculation. The letters represent animals which received 2 minims of the same suspension.

‡ These animals were killed; all the others died.

and eosin, and the lesions in the congested organs were compared with those in the control.[21] The results are given in table 4.

21. Dr. Hansmann and Dr. Schenken aided us in the interpretation of these sections.

In this experiment the development of tuberculosis seemed very slow in all the animals. One of the animals operated on and its control, which were killed after forty-five days, to our surprise showed no tuberculosis in the liver and very early lesions in the spleen, though the retroperitoneal glands were caseous. As we believed that the organism employed had become attenuated through numerous subcultures, we decided to study two series of animals with partially ligated veins, using the Gluckson strain in one series (experiment H, table 5) and a first culture of organisms obtained from a tuberculous epididymis in the other (experiment I, table 6).

TABLE 6.—*Results of Experiment I* *

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Pathologic Changes†		
			Degree of Congestion of Liver	Tuberculosis	
				Of Liver	Of Spleen
1	4	10	+++	0	0
2 (control)	..	20	..	+	++
3	3	23	++++	0	+
4	5	28	++	+++	+++
5‡	5	28	++++	++	++
6 (control)	..	28	..	+++	+++
7	4	29	+++	++	+++
8 (control)‡	..	29	..	+++	++++
9 (control)	..	30	..	+	++
10 (control)	..	32	..	+	++
11‡	5	33	+++	+++	+++
12 (control)‡	..	33	..	+++	+++
13 (control)	..	33	..	++	+++
14 (control)	..	34	..	+++	++++
15	5	35	++	++	++
16 (control)	..	35	..	+++	+++
17	4	45	++++	+	+
18	3	45	++++	+++	+++

* All the animals in this series received 2 minims of the same suspension.
† The degree of congestion and of tuberculosis is indicated as in table 4.
‡ These animals were killed; all the others died.

PARTIAL LIGATION OF THE INFERIOR VENA CAVA OF THE GUINEA-PIG

In the experiments with partial ligation the operative technic was altered somewhat. It was found to be of considerable advantage to elevate the animal board about 60 degrees. In this position, the liver fell away from the diaphragm by gravity, eliminating the necessity of retraction or of manipulating the abdominal contents in any way. This advantage plus that of the partial ligation of the vena cava lowered our operative mortality from 80 to 20 per cent. The partial ligation was effected by incorporating a ligature carrier (1.5 mm. in diameter) in the ligature. When the hook was removed, a lumen in the vein 1.5 mm. in diameter remained. The size of the lumen was checked at all postmortem examinations. The evidences of congestion in the liver and spleen after this method seemed just as marked as after complete ligation.

COMMENT

In most of the animals the tuberculosis of the spleen appeared greater in amount and more advanced than that of the liver. It never appeared to be less extensive in the spleen.

It would seem as one examines the tables, particularly table 6 (experiment I), that an occasional animal that lived a long time showed relatively less tuberculosis. No significance can be attached to this, however, in respect to the animals operated on, because the controls exhibited the same phenomenon. A possible explanation is that the guinea-pigs varied slightly in susceptibility to tuberculosis or that the dosage varied in spite of our attempt to standardize it.

In studying the sections from the animals showing more advanced changes the impression was obtained that the amount of tuberculosis in the animals operated on was definitely less than in the controls after a corresponding period. There was no difference, however, in the size or the histologic appearance of the individual lesions. On this basis it is our impression that the fewer lesions can be attributed to the retarded or congested circulation. Our interpretation of the findings is that congestion retarded the development of tuberculosis in respect to the gross number of lesions but that it had no effect on the growth and progress of the existing lesions, and the end-result was the same in all animals.

In the experiment made after partial ligation of the vena cava, the results did not differ for the two strains of tubercle bacilli.

CONCLUSIONS

Passive congestion produced by complete or partial ligation of the inferior vena cava of the guinea-pig has no influence on the progress or the histologic characteristics of tuberculosis in the liver and spleen produced by human tubercle bacilli.

The number of lesions is smaller in congested organs than in the corresponding organs in the controls, a fact which can probably be attributed to the retarded circulation.

SURFACE TEMPERATURE TEST IN VASCULAR OCCLUSION AND VASOMOTOR SPASM

ITS VALUE IN RELATION TO SYMPATHECTOMY

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The general assumption that the pathologic conditions which are amenable to treatment by sympathectomy are dependent on vasomotor spasm has led to the estimation of surface temperature as an index of the potential degree of vascular release. The skin temperature and the potential rise have been investigated by exposure to high environmental temperatures and by blockage of the vasomotor impulses by the injection of procaine hydrochloride into the peripheral nerves or by the use of spinal anesthesia.

From a study of these methods it has been found that there is a gradation of the skin temperature from the trunk to the extremities in normal persons, which may be termed the vasomotor gradient, and that exposure of the body to a uniform warm air temperature of from 34 to 38 C. (93.2 to 100.4 F.) produces generalized vasodilatation with equalization of the temperatures of the central and distal surfaces. Coller and Maddock [1] have shown that in healthy persons exposure of the body to uniform high environmental temperatures results in a rise of skin temperature to an average level in men of from 34 to 35 C. (93.2 to 95 F.) and in women of from 35 to 36 C. (95 to 96.8 F.).

The application of similar tests of vasodepression in patients suffering from vascular diseases has been shown to result in a failure of the surface temperature to rise to the average levels attained in normal persons, and the difference between the maximum surface temperatures in the normal and in the pathologic cases is regarded as an index of the degree of vascular occlusion. As the result of their studies, Coller and Maddock divided the cases of vascular disease into three groups. In the first there is a slight change or no change following the application of tests of vasodepression. In this group they placed advanced cases of thrombo-angiitis obliterans and of peripheral arteritis. They regarded cases in this group as evidencing definite vascular occlusion and stated that sympathectomy is contraindicated. In the second group, in which there is a normal rise in surface temperature, taken as an indication of

1. Coller, F. A., and Maddock, W. G.: Ann. Surg. **96**:719 (Oct.) 1932.

the total absence of arterial block, they considered that sympathectomy offers the greatest possibility of relief. This group shows a combination of occlusion and vasospasticity.

The importance attached to the observation of a rise of surface temperature in the estimation of the prognosis and operability in cases in which sympathectomy is indicated suggested the study of the recovery period in such cases in relation to the surface thermal changes. The outcome of these observations and the detailed investigation of a case of vascular occlusion have shown that the foregoing conclusions must be modified.

Before discussing these results it should be noted that all sensitive methods for the estimation of surface temperature depend on thermoelectric principles, the pole or poles of the apparatus being applied to the skin or introduced into the dermal tissue, as practiced by Uffreduzzi,[2] and that the slight local variations are rapidly recorded by the galvanometer.

The details of a case of vascular occlusion are as follows:

REPORT OF CASE

A man, aged 59, noticed an ulcer on the fourth toe of the left foot about Easter, 1930. He thought that it was caused by the pressure of his clog. In August of the same year a constant aching and burning commenced, and the ulcer remained unhealed. In December the left foot became cyanosed and generally painful and was markedly swollen after walking. On Feb. 9, 1931, he was admitted to the hospital. There was complete gangrene of the terminal phalanx of the fourth toe, and the third toe was congested and showed two hemorrhagic blisters. The entire foot was slightly swollen and felt warmer than the right foot. The skin over the dorsum was cyanosed. The surface temperature readings, taken by the Campbell-Smith platinum resistance thermometer, are given in table 1.

Perifemoral sympathectomy was performed on February 24. There was no further change of surface temperature. The gangrene reached a stationary condition in the fourth and second digits, which were amputated on March 12. After a period in the hospital for convalescence he was discharged. He was free from pain; the amputation scar was healed, and the skin of the foot was a normal pink on exposure to warm air. In July, slight pain returned in the foot, which varied in severity throughout 1931 until June, 1932, when the foot again became swollen and the amputation scar of the second toe broke down, forming a small discharging ulcer.

The patient was readmitted to the hospital on October 2. There was a small hypersensitive ulcer on the plantar aspect of the base of the second toe. The foot was deeply cyanosed, but this condition disappeared on elevation. Apart from this, the skin over the remainder of the foot had a normal appearance. It was noticed that deep pressure in the popliteal fossa caused a rapid change in the tint of the skin, with almost immediate blanching of the blood vessels of the surface. This suggested that there was a marked degree of vasomotor spasm. The patient was accordingly tested for vascular release by exposure to high environment tempera-

2. Uffreduzzi, O.: Gaz. d. hôp. **101**:265, 1928.

tures under a radiant heat lamp. The average surface temperature over the feet under these conditions was from 35 to 36 C. (95 to 96.8 F.). A further estimation was carried out under spinal anesthesia, which resulted in a rise in the temperature of both legs of between 6 and 8 degrees C. (11 and 14 F.), a considerable rise for a man of this age and type.

On October 5 lumbar ganglionectomy was performed on the left side. The third and fourth ganglions and a portion of the second ganglion were excised, and the chain was divided below the fourth ganglion. After the operation the estimation of surface temperature showed an average rise of from 3 to 4 degrees C. (5 to 7 F.) over the affected foot. The color of the skin was normal, and on release of local pressure there was rapid filling of the surface vessels, indicating an active cutaneous circulation. Clinically, the operation was a complete failure. The pain increased in severity, and the discharge from the ulcer persisted.

In view of the severity of the pain, the popliteal nerves were exposed under procaine hydrochloride anesthesia, and an injection of a 30 per cent solution of antipyrine containing 2 per cent procaine hydrochloride was made. At the same time the popliteal artery was stripped, and an injection of absolute alcohol was made in its sheath in view of the possibility of inadequate ganglionectomy. It was

TABLE 1.—*Surface Temperature Readings in a Patient with Vascular Occlusion in the Lower Left Extremity (C.)*

	Middle of Dorsum	Ball of Great Toe	Middle of Heel	Anterior Middle of Leg	Posterior Middle of Leg	Patella	Anterior Middle of Thigh	Posterior Middle of Thigh
Left foot...	33	31.5	32.5	31.5	33.0	34	33	35.5
Right foot..	30	29.0	30.5	31.5	31.5	31	33	35.0

observed that there was no phase of contraction during this procedure, which had been marked at the primary perifemoral sympathectomy. Pain was relieved by these methods for only twelve hours, and there was no further rise in surface temperature.

On November 3 the leg was amputated on account of the intolerable pain. Up to this time the only surface lesion was the small discharging ulcer at the distal end of the plantar surface. The changes in surface temperature were maintained to the time of amputation.

Immediately after the amputation I injected iodized poppy-seed oil 40 per cent into the anterior and posterior tibial arteries and took roentgenograms of the foot. These showed that the anterior tibial artery was blocked at about the level of the anterior annular ligament and that the posterior tibial artery was obstructed near its bifurcation into the external and internal plantar arteries. The blood supply of the foot was carried on by the peroneal and malleolar vessels, and the roentgenogram showed a free injection of the vessels of the surface around the heel, although the iodized oil had not penetrated into the vessels of the more distal surfaces.

The arteries were dissected, and the organic occlusion was found to correspond with the roentgenologic appearance. It was noted that the dermal structures over the entire foot, with the exception of the ulcerated area, were well supplied with blood. On the other hand, all the structures between the plantar fascia and the arch of the tarsus were completely necrotic, consisting of a pulpacious mass slowly liquefying and discharging through the peripheral ulcer.

In the case described there is definite evidence of two factors operative on the vascular system: (1) endarteritis, causing a complete blockage of the main peripheral arteries, and (2) generalized freedom of the

Roentgenograms of the foot taken after amputation, showing blocking of the anterior tibial artery and obstruction of the posterior artery: *A*, anterior view; *B*, lateral view, showing in addition congestion of the vessels of the surface around the heel.

dermal blood vessels from vascular occlusion, but a marked degree of vasospasticity prior to sympathectomy. The result of the first factor was slow aseptic gangrene of the subfascial plantar tissues, accom-

panied by intense irritation of the common sensory nerves. The second factor produced preoperative variations in the tint of the skin and a normal thermal response to high environmental temperatures, together with a maximal vascular release under spinal anesthesia, and absence of the occlusive index and good filling of the surface on the release of pressure.

It is evident that the sensitivity of thermo-electrical methods of determining changes in surface temperature gives results that are dependent on the response of the blood vessels of the surface. The

TABLE 2.—*Average Rise in Surface Temperature Compared with Time Required for Healing and Recovery Following Ganglionectomy and Periarterial Sympathectomy*

Case	Operation	Average Post-operative Rise in Temperature (Degrees, C.)	Period of Healing of Lesion	Period of Subsidence of Pain	Period of Freedom from Recurrence
1	Cervical ganglion-ectomy, left	0 to 1	Gangrene of index finger, 2-3 weeks	24 hours	21 months
2	Lumbar ganglion-ectomy, right	0.75 to 1.25	Deep plantar ulcer; healed, 2 weeks; filled, 6 weeks	Immediate	3 months
3	Lumbar ganglion-ectomy, right	2	Deep plantar ulcer; healed, 1 week; filled, 5 weeks	Immediate	7 months
4	Lumbar ganglion-ectomy, left	6	Pain crisis	Immediate	26 months
5	Periarterial sympathectomy	0.5 to 1; none after 3 weeks	Gangrene of terminal phalanx,of second toe, 2-3 weeks	7 to 10 days	24 months
6	Periarterial sympathectomy	0.5; none after 2 weeks	Gangrene of terminal phalanx of fourth toe, 3-4 weeks	Immediate	6 months
7	Periarterial sympathectomy	0.5 to 1; none after 10 days	Chronic ulcer of leg, 8 weeks	24 hours	24 months
8	Periarterial sympathectomy	0.5 to 1; none after 3-4 weeks	Chronic ulcer of leg, 16 days	24-48 hours	18 months
9	Periarterial sympathectomy	0.5; none after 12 days	Ununited fracture of tibia, 3-4 weeks, with excessive callus		

estimation of the rise in skin temperature in occlusive vascular disease as a criterion of operability introduces a factor of possible error. Thrombo-angiitis obliterans attacks first the principal distal arteries, which become obstructed long before the dermal vessels; hence the application of the temperature tests may lead to deductions based on vascular release of the dermal vessels in the presence of completely occluded deep arteries. On the other hand, the investigation of the potential vascular release based on the rise of dermal temperature must obviously be a reliable and valuable procedure in judging operability in cases of vasospasticity, and in this particular sphere I agree with the observations of Coller and Maddock that the more satisfactory method of estimating these changes is by the use of the high environmental temperature tests. The unpleasant psychic effects of peripheral nerve block and spinal

anesthesia make the employment of these tests objectionable to some patients, and, further, a fall in blood pressure and a correspondingly inadequate thermal response frequently follow their use.

The subject may be studied from another aspect. In table 2 I have indicated the average rise in surface temperature after ganglionectomy and periarterial sympathectomy in nine cases, the clinical results of which were classed as good. The relative time for recovery from the symptoms and for the healing of the peripheral lesion is compared with the rise in surface temperature and the period during which the hyperthermia was maintained.

TABLE 3.—*Average Rise in Temperature in Eleven Cases of Sympathectomy for Vascular Occlusion Recorded by Telford and Stopford*

Analysis of results		Number
Good		8
Fair		2
Failure		1
Total		11
Average rise in the temperature of the skin		**Degrees, C.**
Good results	Right and left sides	2.47
Fair results	Right and left sides	2.27
Good results	Right side only	2.243
Good results	Left side only	2.675
Fair results	Right side only	2.55
Fair results	Left side only	2
Average rise in the temperature of the skin in the limb which exhibited the more serious lesion		
Good results		1.725
Average rise in the temperature of the skin in nine cases of sympathectomy for miscellaneous conditions the results of which are classed as good (own cases)		
Average of highest temperatures	(approximately)	1.58
Average of lowest temperatures	(approximately)	1.39

It will be observed that in the cases in which the rise in temperature was of a minor degree, there was progressive healing of the distal lesion and cessation of pain, and that in several cases periarterial sympathectomy gave complete relief within from one to two years. These results form a striking contrast to the hyperthermia observed in the case already discussed. Moreover, another point may be noted from table 2: In several cases the comparatively small degree of hyperthermia ceased long before the healing of the surface lesion.

In table 3 I have set down the average rise in surface temperature in a series of cases which were reported by Telford and Stopford.[3] It will be seen that, taking the average rise of temperature in the cases in which the results were classed as good in the affected limb which showed the more serious clinical symptoms, the average hyperthermia

3. Telford, E., and Stopford, J. S. B.: Brit. M. J. **1**:1116 (June 18) 1932; ibid. **1**:173 (Feb. 4) 1933.

was less than that in the cases in which the clinical results were classed as fair. This compares favorably with the average hyperthermia observed in the nine cases classed as good in my own series.

These facts suggest that, although vascular dilatation must play some part in the healing of peripheral lesions, it is by no means the sole factor. There is evidence to show that sympathectomy may directly alter the physiochemical balance of the tissue cells, and that slight changes of the hydrogen ion concentration may occur after this procedure.

Jung and Leriche described reactions in sympathectomy wounds varying from acid to alkaline, whereas in wounds that had not been subjected to sympathectomy the reaction was always acid. In this association the work of Fischer [4] has demonstrated the remarkable sensitivity of fibroblasts to the slight changes in the hydrogen ion concentration, and Balint and Weiss [5] have shown the striking effect of variation of the p_H of the tissue fluids on healing wounds. It is possible that some such change occurs at the margin of the tissue cells after sympathectomy and that this change of the ion concentration determines the nature of the inflammatory reaction, the destructive phase giving place to the assimilative one.

CONCLUSIONS

It is concluded that the estimation of the potential rise in surface temperature is a useful index of the degree of vasospasticity of the dermal blood vessels and can be applied particularly in pure vasomotor conditions, such as Raynaud's disease. On the other hand, the application of these tests in cases of occlusive vascular disease, such as thrombo-angiitis obliterans, is of very slight value for the following reasons: first, on account of the factor of possible error; second, because considerable hyperthermia is not necessary for the relief of the symptoms or the healing of the peripheral lesions, and third, because although these cases exhibit varying degrees of vasospasticity of the surface blood vessels ganglionectomy is by no means able to overcome the effects of a complete block of the deeper vessels (as shown in the case reported in this article), and it is suggested that some change other than mere vasodilatation may be necessary for a successful result from sympathectomy.

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4. Fischer, A.: J. Exper. Med. **34**:447, 1921.

5. Balint, R., and Weiss, S.: Tissue Proliferation and Acid Base Equilibrium, translated by F. Morena and G. C. Pether, London, Constable & Co., Ltd., 1932.

OBSTRUCTIVE JAUNDICE

DUE TO DIFFUSE CONTRACTURE OF THE EXTRAHEPATIC BILE DUCTS

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The problem of benign stricture of the bile ducts is one which in recent years has come to occupy a position of major importance in the field of abdominal surgery, as is attested by the numerous papers on the subject which may be found in the current literature. While a few decades ago clinical observations and case reports were concerned chiefly with the so-called congenital strictures which are of interest to the pathologist but usually surgically hopeless, today the acquired type of stricture assumes the predominant rôle. The reasons for this are: first, the greater frequency with which these acquired strictures are encountered, probably owing to the more widespread practice of cholecystectomy; second, the chance of affording relief by surgical therapy now possible with the development of appropriate operative procedures for dealing with such lesions, and third, the importance of their prevention.

For the most part the congenital strictures do not concern the surgeon. This condition is characterized by complete biliary obstruction appearing a short time after birth, and it ordinarily soon leads to a fatal termination. The situation of the obstruction and the type of lesion may show the utmost variation in different cases, but obliteration of the lower end of the common bile duct or complete occlusion of the whole duct seems to be found most often, while abnormalities of the hepatic duct are perhaps second in frequency. The pancreatic duct is only rarely affected. Along with these changes in the major ducts, obliteration of the cystic duct or even absence of the gallbladder is a frequent accompaniment. Occasionally a patient with a congenital stricture of the common duct may survive until adult life; interesting cases have been reported by Treves,[1] Mathieu [2] and Judd and Burden.[3] While

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From the Department of Surgery, University of Michigan.

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1. Treves, F.: A Case of Jaundice of 16 Years' Standing Treated by Operation, Practitioner **62**:18 (Jan.) 1899.

2. Mathieu, Paul: Retrécissements non néoplasiques des voies biliares principales, Rev. de chir. **37**:61, 1908.

3. Judd, E. S., and Burden, V. G.: Benign Stricture of the Bile Ducts, Arch. Surg. **11**:459 (Sept.) 1925.

the nature of the pathologic process of these strictures is not clearly understood, it has been suggested by Moynihan [4] and Rolleston [5] that during fetal life, poisons developed in the body of the mother are carried to the liver of the fetus, provoking a combination of cirrhosis and cholangeitis, the end-result being an obliterative cicatrization of the ducts. Some doubt may be cast on this view by the observations of Feldman and Lawson [6] in 1924 who noted the presence of congenital stricture in one of a pair of binovular twins, the fellow twin being quite normal. Other authors, notably Rolleston,[7] have reported cases of congenital stricture of the common duct which they believed were caused by syphilis.

The second group, or the acquired type of stricture, is the one in which we are chiefly interested. Here we have more positive information regarding etiology, and considerable clinical experience has accumulated concerning operative treatment. The acquired strictures may be subdivided into a traumatic and an inflammatory group. Of the traumatic type, by far the greatest number of instances are those in which injury to the hepatic or common duct during cholecystectomy has occurred. This injury may consist in an actual severing or ligation of the duct or even excision of a segment; wounding of the duct with the production of an external biliary fistula and subsequent cicatrization; or perhaps most commonly, the placement of the ligature of the cystic duct too close to the common duct so as to compromise its lumen when the ligature is tied. In other instances, it has been suggested that an abnormal amount of scar tissue may develop about the duct from the use of too large or too heavy gauze drains, with the ends left close to the duct. Again, damage to the circulation of the duct from an overzealous denudation at the time of operation has been mentioned. These strictures naturally are usually located near the junction of the cystic and hepatic ducts and are fairly circumscribed; frequently there is a segment of normal duct above and below the point of obstruction, a fortunate finding when surgical reconstruction of the duct is to be done.

The inflammatory variety of acquired stricture is commonly regarded as due to a localized cicatrix presumably caused by an initial ulceration of the mucous membrane by the passage of a gallstone or to impaction of a stone in the wall of the duct with resultant injury and subsequent

4. Moynihan, quoted by Judd.[3]

5. Rolleston, H. G.: Diseases of the Liver, Gall Bladder and Bile Ducts, London, The Macmillan Company, 1912.

6. Feldman, William, and Lawson, M. A.: A Case of "Congenital" Occlusion of the Common Hepatic Duct in a Twin Baby, with an Indirect van den Bergh Reaction, Lancet **2**:113 (July 19) 1924.

7. Rolleston, H. G.: Congenital Syphilitic Obstruction of the Common Bile Duct, Brit. M. J. **2**:947, 1907.

contraction of the scar tissue during the healing process. Such strictures are usually quite localized and found in a duct which at other points is within normal limits.

According to Judd [8] these etiologic factors of initial injury have been greatly overrated, and he believes that in many of these so-called acquired inflammatory and traumatic strictures, the process is fundamentally an obliterative cholangeitis. In support of his contention he cited cases in which the clinical evidence of stricture did not appear until many months or even years after the cholecystectomy.

Finally, there is another and fortunately more unusual variety of obstruction of the common duct, namely, the diffuse fibrosis of the entire system of extrahepatic ducts with ultimate contracture whereby the ducts are converted into a small thick-walled tube with severe compression or even occlusion of the lumen. This type of lesion in all probability should be regarded as an obliterative cholangeitis, since the factors of previous operations or preexisting gallstones can be excluded in the majority of the reported cases. As an example of this type, we relate the history of such a case in which the patient was only recently under our care.

REPORT OF CASE

CASE 1.—*History.*—O. P., an American tanner, aged 35, was admitted on Oct. 12, 1932, with a complaint of "stone in the common duct."

His health had been good until seven weeks prior to admission to the hospital, at which time he first experienced an attack of rather severe acute abdominal pain, which was colicky and localized to the right upper quadrant of the abdomen. The pain did not radiate. This first attack lasted for several hours, and slight nausea and vomiting were associated with the pain. The symptoms continued with less severity and he was required to give up his work and go to bed. The daily nausea and vomiting continued until one week before admission. The vomitus was greenish and occasionally it was streaked with blood. He had had no chills or fever as far as he was aware. Three weeks before admission, jaundice was noted for the first time. Along with this the patient noticed that the urine was dark, but he did not know whether the stools had been clay colored. The pain in the right upper quadrant came on two or three times a day, remaining quite well localized and being definitely colicky. It seemed to be aggravated by exercise, but had not progressed in severity. At the beginning of his illness he was seen by a local physician who told him that he had a stone in the common duct. His appetite had been poor since the onset of the trouble. He estimated that he had lost about 30 pounds (13.6 Kg.) during the seven weeks of his illness. His health had always been exceptionally good in the past. There had been no injuries or surgical operations. He was a moderate user of tobacco, but not of alcohol.

Examination.—The patient was a well developed and well nourished adult who appeared to have lost considerable weight and who was quite dehydrated at the time of admission. The skin and sclerae showed deep jaundice, and there were a

8. Judd, E. Starr: Stricture of the Common Bile Duct, Ann. Surg. **84**:404 (Sept.) 1926.

number of excoriations from scratching owing to the intense pruritus. The teeth were in poor condition, with marked oral sepsis. The tonsils were hypertrophic and septic. Otherwise, the head, neck and thorax were normal.

The panniculus was abundant, the anterior abdominal wall being slightly above the level of the costal margin. There was slight generalized tenderness, but otherwise the abdominal examination gave negative results. The gallbladder was not palpable.

The temperature, pulse and respiration were normal on admission and remained essentially so during the first few days in the hospital, with a slight rise in temperature to 99 or 100 F. in the afternoon.

Laboratory Examinations.—The Kahn test was negative. Examination of the blood showed a hemoglobin content of 59 per cent and a white cell count of 6,400. The bleeding time was four and a half minutes and clotting time eight minutes. The urine was normal except for the presence of bile in several specimens examined. The stools were clay colored. The blood bilirubin was 75 mg. per thousand cubic centimeters (direct van den Bergh test). A gastro-intestinal roentgen examination was made which revealed no organic disturbance in the upper portion of the alimentary tract. On account of the obstructive jaundice, cholecystograms were not made.

Preoperative Treatment.—The patient was given an abundance of fluids, a diet high in carbohydrate with calcium and dextrose administered intravenously over a period of eight days. The itching was considerably relieved by antipruritic treatment.

Comment.—This was a case of a healthy young man with a fairly short history of what seemed to be gallstone colic with jaundice developing subsequently, which suggested the likelihood of a stone in the common duct. It might be noted, however, that the jaundice had not been intermittent, but had continued without remission during the three weeks since it had first appeared. Although chills were not present there was a slight rise in temperature in the afternoon. The possibility of a pancreatic neoplasm was considered, but this was not regarded as very probable.

Operation (by H. K. R.).—On Oct. 20, under avertin, nitrous oxide and oxygen anesthesia, an upper right rectus incision was made. All tissues were found to be deeply jaundiced. The liver was normal in size, but blackish, suggesting biliary obstruction of fairly long standing. The wall of the gallbladder was thickened and the gallbladder was contracted, but it did not contain stones. The foramen of Winslow was patent, but exact identification of the common and cystic ducts was difficult, owing to an inflammatory process about the ducts. There was no evidence of dilatation of the common or hepatic ducts, and no stones could be felt on palpation. Attempts to aspirate the common duct were unsuccessful; therefore, in order to be very certain of the point of junction of the cystic and common duct, the gallbladder was dissected off of the liver and followed as a guide to the common duct. At a point just distal to the junction of the cystic and common ducts, by means of a very fine hypodermic needle, a drop or two of bile could be obtained. Following this, the duct was opened in a longitudinal direction. This was a difficult procedure because, as the incision was made, it was found that the common duct was so contracted as to be only a small fibrous cord with a thick, tough wall and

almost complete obliteration of the lumen. When the lumen was opened, a minute quantity of bile escaped. Probing of the duct could be done with nothing larger than a fine silver wire probe. This could be passed downward into the duodenum and upward into the hepatic ducts without encountering any definite point of complete obstruction. A uterine sound or the smallest bougie could not be introduced on account of the small size of the lumen. At this point an unfortunate happening occurred. Owing to the tension on this very slender fibrous duct in the attempt to probe it, the duct snapped completely in two at the point at which it had been opened. Because of the extreme narrowing of the lumen of the duct, it was impossible to reconstruct it over a T-tube or any small tube, as none was of sufficiently small caliber to be introduced. Likewise no catheter was small enough to permit its introduction into the cut end of the upper segment for the purpose of external drainage. As the operation had been somewhat prolonged, owing to this accident, and since the patient's condition was failing, in desperation the lower end of the duct was closed and the upper end brought up through the peritoneum, and the gallbladder necessarily removed. This part of the abdomen was then quarantined by the Coffey method of drainage and the abdomen was closed. Immediately a transfusion of blood was given and dextrose was administered intravenously continuously thereafter. His condition during the afternoon was poor, and at 6 o'clock a second transfusion of blood was given, but he rapidiy became worse and died at 8:30 p. m.

Pathologic Report.—The report on the specimen removed (gallbladder) at operation was: "Chronic cholecystitis with diffuse fibrosis of the gallbladder wall. No stones were present. A lymph node included in the material showed chronic lymphadenitis of the sinus epithelium."

Necropsy.—A postmortem examination showed that the entire system of extrahepatic ducts had undergone extensive fibrosis with extreme narrowing of the lumen. The process included the common duct, the common hepatic duct and both right and left hepatic ducts to almost the same degree, with possibly more extensive alteration in the hepatic ducts than in the common duct. The liver showed a biliary cirrhosis. No other changes of importance were revealed. Death was undoubtedly due to shock from the prolonged operation in a patient who was a poor risk.

The unusual findings at operation called to mind an earlier operative experience in a somewhat similar case encountered about nine years before, a detailed account of which will be given (case 2). It also stimulated us to undertake a survey of the literature on the subject of stricture of the bile ducts, as at operation a condition had been discovered which was wholly unexpected and one in which the likelihood of cure by surgical intervention seemed highly improbable. We shall endeavor to give a short account of the more important recorded observations.

CASES IN THE LITERATURE

In 1927 Miller[9] reported a case very similar to ours in all particulars. Miller's patient was a man, 40 years of age, who presented himself with a history of recurrent attacks of severe pain in the upper part of the abdomen of five months' dura-

9. Miller, Robert T., Jr.: Benign Stricture of Bile Ducts, Ann. Surg. **86**:296 (Aug.) 1927.

tion, these attacks usually being preceded by abdominal distress and associated with nausea and vomiting, finally terminating in a period of malaise lasting for two or three days. Symptoms of indigestion had become increasingly more severe. There had been a loss of 15 pounds (6.8 Kg.) caused by jaundice, which had developed three weeks before admission. The examination showed a well nourished man with moderate jaundice, slight enlargement of the liver, but without tenderness, muscle spasm or palpable masses in the abdomen. While the patient was in the hospital the temperature varied from 97.6 to 99.2 F. and the leukocyte count was normal. The gastro-intestinal tract was found to be normal on roentgen examination, and a roentgenogram of the gallbladder was negative for stones. The urine showed a positive reaction for bile, and the stools were clay colored, chemical tests showing only a small quantity of bile. The guaiac test was negative. The condition was thought to be a stone in the common duct, while the possibility of neoplasm was considered. At operation a chronically inflamed gallbladder was found without stones. Palpation of the common duct suggested a superficial saphenous vein occluded by organized clots. The whole duct was felt as a hard cord of slightly less than normal size. "The duct was opened, its wall was found to be greatly thickened throughout, its lumen much diminished in size and lying in it were a few flakes of deep colored soft débris. No bile came from the duct until a probe had been somewhat forcibly inserted into the hepatic duct, whereupon a small amount of very faintly colored secretion appeared. It was impossible to pass anything larger than a very fine probe into the duodenum, the lumen of the duct being all but occluded by its thickened wall. The exact nature of the change in the wall of the duct was not understood but because of bothersome bleeding no specimen was excised for diagnosis." The duct was closed and a cholecystogastrostomy done. The patient recovered from the operation, and all of his symptoms were relieved.

Pierre Delbet[10] in 1924 reported another almost identical case. His patient, a man of 48 years, complained of recurrent attacks of epigastric pain with nausea and vomiting of two years' duration, while jaundice had appeared ten days before the examination. Examination revealed extreme epigastric tenderness and muscle spasm. The stools were light colored. A diagnosis of stone in the common duct was made and a laparotomy performed; at this time a thin-walled gallbladder was found which was moderately tense and buried in light adhesions. The common duct was contracted, and on being incised it was found to have extremely thick walls with a very small lumen, although a fine catheter could be passed through the lower end of the duct into the duodenum. The catheter could not be passed to the liver, but evidently the duct was not completely occluded. The operation was therefore concluded by anastomosing the gallbladder to the duodenum. Convalescence was uneventful, and the jaundice disappeared.

Lafourcade[11] in 1925 reported the case of a man, 58 years old, who had had attacks of gallstone colic for thirty years. Jaundice had gradually developed eight months before admission. Examination showed the liver to be slightly enlarged, and the stools were clay colored, while the urine contained bile. A diagnosis of stone in the common duct was made and an operation performed. At this time the gallbladder was found to be contracted and buried in adhesions. The common duct

10. Delbet, Pierre: Bull. et mém. Soc. nat. de chir. **50**:1144, 1924.
11. Lafourcade, L.: Bull. et mém. Soc. nat. de chir. **51**:828, 1925.

was extremely indurated throughout its course, and when opened the wall was found much thickened, owing to general fibrosis. Lafourcade stated that the wall of the duct was 0.5 cm. in thickness and the lumen so small that only with the greatest difficulty could a stilet be inserted. In this case, the hepatic duct was apparently not very abnormal, for Lafourcade cut it across and inserted a rubber tube, the distal end of which was carried into the duodenum. The patient died forty-eight hours later, but permission for autopsy was not granted.

Dr. Allen O. Whipple,[12] of New York, discussed the case of a woman, aged 50, with pernicous anemia who came to him with a history of digestive symptoms and jaundice. The jaundice had been complete for two months before operation. At operation the gallbladder was found to be collapsed, the common duct was felt as a thickened cord throughout its entire length, including the common hepatic duct, and no bulging of the right or left hepatic duct could be made out. Because of the inability to locate a dilated duct, no attempt was made to drain either the gallbladder or the duct system. The liver showed an extensive cirrhosis of the biliary type which was proved by microscopic section. The wound was closed without further procedure and on the ninth day after the operation the patient began to show some bile in the stools and continued to recover without interruption. She remained well as far as was known.

These cases of Miller, Delbet, and Whipple seem to have been quite similar to case 1 in that the hepatic duct as well as the common duct was involved in the inflammatory process, while the case reported by Lafourcade differed slightly in that the hepatic duct did not show notable change. In considering the etiology of this condition, the striking thing about all of these cases is the absence of any previous abdominal operations and also the absence of stones in both the gallbladder and the ducts at the time of operation. The factor of operative trauma can be excluded, while damage to the ducts from the passage of stones at an earlier date seems highly improbable. Likewise the diffuse and uniform character of the process seems quite incompatible with such a causative agent. We are left, then, with the alternative of explaining the process on the basis of an obliterative cholangeitis which had led to ultimate diffuse fibrosis and contracture. This view seems to be substantiated in our case in which microscopic examination of the duct was possible, as the histologic examination showed a marked fibrosis of the walls of the ducts indicating a chronic cholangeitis with the process still showing some degree of activity (fig. 1). It is usual in infections of the biliary tract for the process to gain a foothold and produce the greatest damage in the wall of the gallbladder itself, while the ducts show a rather remarkable ability to resist infection. It would seem that in these rare cases, the gallbladder and the ducts shared alike in the inflam-

12. Whipple, Allen O.: Tr. Am. S. A. **45**:143, 1927.

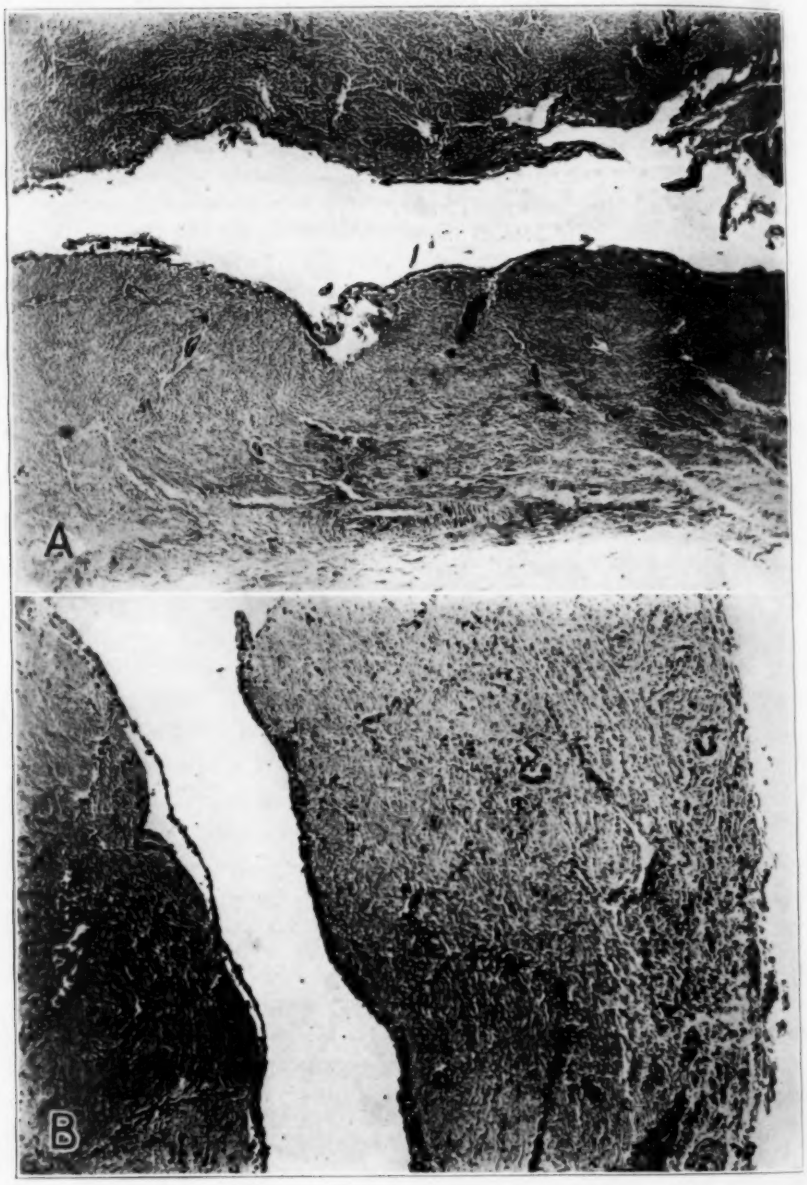

Fig. 1 (case 1).—*A*, fibrosis of the hepatic duct; *B*, the same process in the common duct; × 80.

matory process and that even before stones have had a chance to form in the gallbladder, the maximum damage has been produced in the wall of the extrahepatic ducts, while the inflammatory process in the wall of the gallbladder has progressed to a lesser degree. We now present the report of the second case, to which reference has been made.

CASE 2.—*History.*—Mrs. N. G., a housewife, 53 years old, was admitted to the hospital on March 3, 1924, complaining of attacks of abdominal pain, gas and jaundice. She had never been very strong and had had all of the usual contagious diseases and frequent attacks of infections of the upper respiratory tract. Three years before, she contracted typhoid fever. The attacks of gas, flatulence and epigastric pain began about four years before admission. The pain tended to be more severe at night. In May, 1923, a cholecystectomy for gallstones was done. Since then she had never felt entirely well. There had been attacks of pain, gas and jaundice with chills and fever. The temperature frequently reached 104 F. Jaundice developed four weeks prior to admission.

Physical Examination.—The patient was a nervous slender woman of medium stature. The skin and sclerae showed marked jaundice. Abdominal examination revealed the scar of a former right rectus incision which was well healed but showed a slight tendency to keloid formation. There were no palpable masses and no muscle spasm.

Laboratory Examination.—Urinalysis gave negative results except for the presence of bile. The hemoglobin was 80 per cent, the red cell count, 4,156,000 and the white cell count, 7,300. The stools were clay colored. Examination revealed: no free fat; free starch, 1 plus; few undigested meat fibers; no ova. The coagulation time by the Howell method was twenty minutes.

Comment.—This was a patient with all the signs and symptoms of obstruction of the common duct developing nearly a year after cholecystectomy. On account of the pain and digestive disturbances along with the jaundice, chills and fever, a diagnosis of a stone in the common duct was made and operation recommended.

Operation (by Dr. F. A. Coller).—On March 4, under ethylene and oxygen anesthesia, a laparotomy was performed, the incision being made through the old scar. Adhesions were found between the liver and the parietal peritoneum and between the duodenum and transverse colon and the anterior aspect of the liver. The foramen of Winslow was open and an excellent exposure obtained. The common duct was found to be very small throughout its entire extent. It was impossible to pass a no. 8 F. bougie along its course. The duodenum was opened and an attempt made to secure some degree of dilation from this end, but it was impossible to pass even the smallest bougie into the common duct. The pancreatic duct was apparently somewhat dilated, as it could be probed throughout its entire extent with a no. 10 F. bougie. Absolutely no dilatation of the common duct existed up to the point where it went into the liver. There were enlarged glands along the course of the common duct, varying from 1 to 2 cm. in diameter. There was absolutely no evidence of any stone, and none could have been present as the examination was entirely adequate. The liver was enlarged, firm and extended three

fingerbreadths below the costal margin. Throughout the right lobe there were areas of increased density which seemed characteristic of isolated areas of cirrhosis. No other abnormalities were found. The duodenum was then closed and the abdominal wall closed in layers about a drain. As a prophylactic measure the patient was given a transfusion of whole blood following the operation although her condition at the time was excellent.

Comment.—At operation, instead of finding dilatation of the common duct as had been expected, quite the reverse was found. The common duct was markedly contracted into a very narrow fibrous tube with enlarged lymph glands along its course. Probing of the duct both from its lower end through the duodenum and through a choledochotomy incision revealed an extremely small lumen with great thickening and contracture of the duct walls. The process was uniform throughout the course of the hepatic and common ducts without stone and without stricture. In the absence of the gallbladder cholecystenterostomy was out of the question, and without dilatation of the hepatic ducts hepaticoduodenostomy was likewise impossible.

Postoperative Course.—On March 5 and 6 the patient's condition was entirely satisfactory. On March 7 abdominal distention began to develop along with nausea and vomiting. At midnight on March 7 the pulse rate had gone up to 140 and the temperature down to 97 F. She was uncomfortable and weak and the following morning was worse. In spite of all treatment, the abdominal distention persisted; she rapidly failed and died at noon on March 8.

Necropsy.—The postmortem examination performed on the day of death disclosed: an acute generalized fibrinopurulent peritonitis with intraperitoneal hemorrhage; chronic ascending cholangeitis with periportal cirrhosis; chronic obstructive jaundice; chronic infection of the common and hepatic ducts; hemorrhagic fat necrosis.

Death was evidently due to postoperative intra-abdominal hemorrhage, easily accounted for on the basis of the chronic jaundice, and peritonitis. The striking finding, however, was the uniform fibrosis and contracture of the hepatic and common ducts without stones and without stricture. Since a complete postmortem examination was made, it seems quite possible to exclude the factor of trauma at the time of the first operation. The entire cystic duct and a tiny stump of the gallbladder were still present, and it is difficult to see how such a process of sclerosis, which was generalized throughout the whole duct system, could be produced by a local injury to the duct. Microscopic examination of the duct likewise tends to further the view that the process was inflammatory in origin, as the microscopic studies revealed a chronic fibrous type of cholangeitis with evidence of moderately active infection still present (fig. 2).

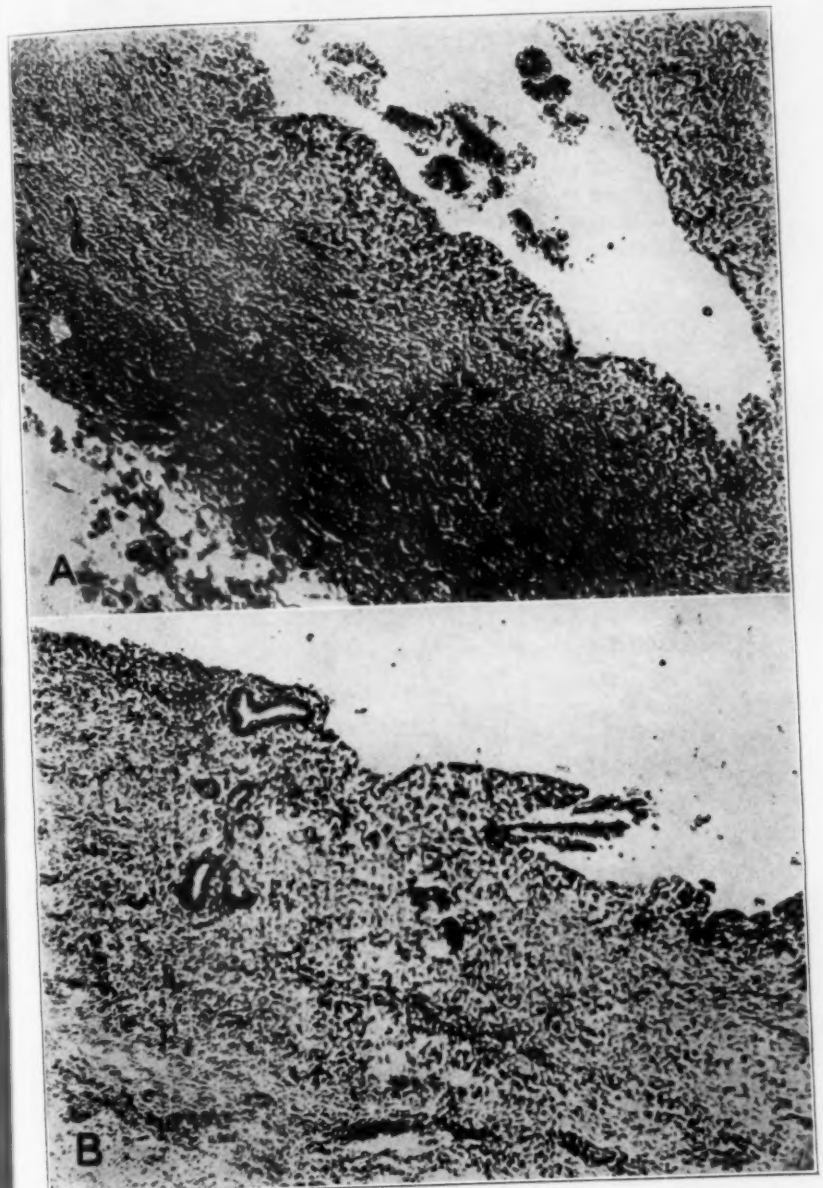

Fig. 2 (case 2).—*A*, obliterating cholangeitis involving the hepatic duct; *B*, similar involvement in the common duct. In this case the process still shows evidence of considerable activity; × 80.

Whipple [12] reported a second case which, because of its resemblance to this last one, should be mentioned here.

A man was found to be a typhoid carrier and for this reason was advised to have his gallbladder removed. At the time of operation the gallbladder as well as the common duct appeared to be the site of chronic inflammation. At the time of the removal of the gallbladder a large portion of the cystic duct was left intact. Convalescence was without event. However, seven or eight months later, jaundice developed and persisted for two or three months. A second operation was performed. At this time complete fibrosis of the common and the common hepatic ducts was found, but there was dilatation of the right hepatic duct, and an anastomosis was made between the right hepatic duct and the duodenum. The patient did well for four days, when a separation at the suture line occurred and peritonitis developed. Whipple stated that he was sure that in this case no trauma had been responsible, because the onset of the jaundice was so delayed. He felt that the condition was undoubtedly the result of a chronic inflammation of the entire efferent duct system.

COMMENT

From the histopathologic standpoint our two cases show essentially the same process in the extrahepatic bile ducts, that is, a chronic obliterating cholangeitis, the process in case 2 being somewhat more active than that in case 1. In both instances the clinical syndrome of obstruction of the common duct with jaundice was produced, and in each instance a clinical diagnosis of stone in the common duct was made.

In case 1 there can be no doubt that the process was inflammatory from the beginning, as the usual factors of operative trauma and irritation or ulceration from stones can be ruled out. In case 2 a cholecystectomy had been performed, and at that time, the gallbladder contained stones. However, the diffuse character of the lesion of the ducts, the absence of stones in the common duct at the time of the second operation and the failure to find any localized stricture would tend to bar from consideration these traumatic factors, while the microscopic studies tend to substantiate the view that we were dealing with a diffuse inflammatory process.

As Miller pointed out, in this group of cases there seems to be nothing characteristic in the clinical findings which might cause one to surmise the actual condition. A preoperative diagnosis in the reported cases was made of obstruction of the common duct probably due to gallstones or cancer, and the true nature of the condition was disclosed only at the time of operation. In fact, there seem to be no reliable criteria by which the diagnosis can be definitely made, although Miller believed that when there is considerable delay in the appearance of jaundice in the patient with a long history of recurrent attacks of biliary colic, one might suspect the condition. Also, the presence of progressive jaundice without remission, in the absence of demonstrable enlargement of the gallbladder, might point to an inflammatory closure of the duct.

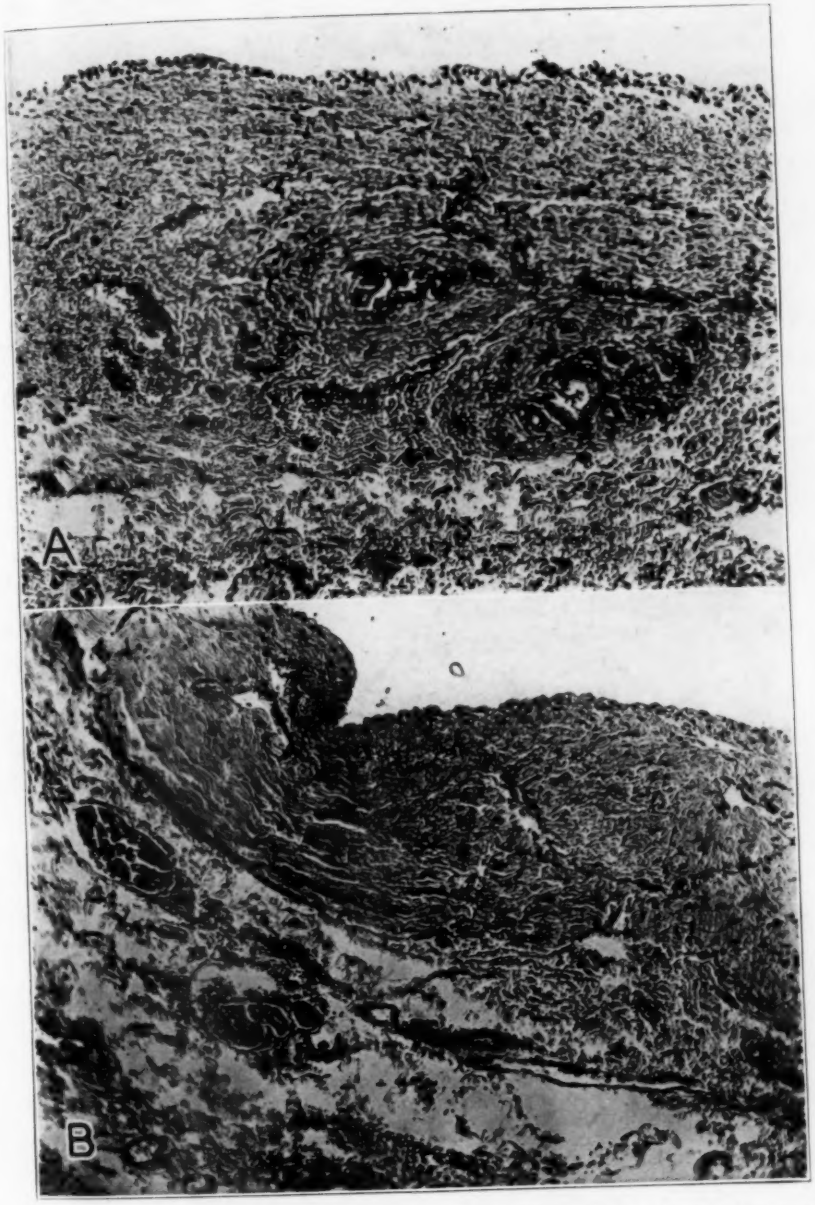

Fig. 3.--Control sections of (*A*) normal hepatic duct and (*B*) normal common duct; × 80.

Regarding therapy, when the entire system of extrahepatic ducts has become involved, the problem of treatment is a difficult one. If technically feasible, and the gallbladder is found to contain bile, cholecystenterostomy seems to be a logical procedure and is probably worth while, although with extreme narrowing of the hepatic ducts it is easy to see how even this may be unsuccessful, while in the case of a small contracted gallbladder such an anastomosis may not be possible. If the hepatic duct remains uninvolved, the decision may be simpler, as in such a case hepaticoduodenostomy might be performed.

TUMORS OF THE SALIVARY GLANDS

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Tumors of the salivary glands constitute a large number of the lesions in the neck and on the face. The so-called mixed cell variety is the most frequent of these growths, although primary carcinomas occur. The close relationship of these lesions to the true malignant growths makes it impossible to separate them. Previous investigations have been directed largely toward a study of the pathogenesis, and but little emphasis has been given to the clinical course. Therefore, a review of the probable pathogenesis, the clinical course and the treatment is given, with a report of twenty-four cases.

According to the appearance of the tumors, various names have been given: fibromyxoma, myxoma, fibromyxo-endothelioma, endothelioma, chondroma, chondrocarcinoma, adenoid cystic epithelioma, cylindroma and many others. Needless to say, they are descriptive only of the type of tissue. The benefit derived from such terms is merely that of a catalog, although the primary purpose of a pathologic classification should be to show, so far as possible, the clinical course and prognosis in an individual case. It must be remembered that benign tumors of the salivary glands may become malignant, and that an incorrect prognosis may be made if they are seen before or during the period of metaplasia.

THEORIES OF FORMATION

Opinions regarding the pathogenesis of the mixed tumors of the salivary glands have been diverse, but, for the most part, these tumors may be considered to be (1) epithelial, (2) fibro-endothelial or (3) fibro-epithelial in origin. Since there is a participation in these tumors of both mesenchymal (connective tissue, mucus and cartilage) and ectodermal (gland, tubules and epithelium) embryonic tissues, such lesions are justly considered to be of the mixed variety. Kux [1] stated that the absence of certain epidermoid cellular content, such as fibrillation of the protoplasm, intercellular bridges and keratohyaline granules, does not speak against their epithelial nature, as epidermoid cellular contents

From the Department of Surgery, Emory University, and the Steiner Clinic.

1. Kux, E.: Histogenesis of So-Called Mixed Tumors of Salivary Glands, Virchows Arch. f. path. Anat. **280**:175, 1931.

cannot be expected in juvenile, nondifferential epithelial cells or in cells that have been transformed into flat epithelium. Concentric formation in mixed tumors may be indicative of epithelial as well as endothelial origin. The demonstration of elastic fibers in the wall of concentric formations may speak in favor of endothelial genesis. If they are derived from endothelium, they originate from the vessels that have undergone hyaline degeneration. In the absence of elastic fibers there is no proof of nonendothelial origin, as they may be destroyed in the walls of the vessels, which have undergone changes.

All these mixed tumors of the salivary glands were originally considered to be carcinomas, especially by German writers. Virchow believed that the cartilage was derived from the metaplasia of connective tissue, although Cohnheim and others considered it to be a remnant of the branchial arches. The endothelial theory was first advanced in 1879 by Hartman, who stated that the polyhedral cells were derived from lymphatic endothelium. This theory was doubted by several investigators, particularly by Hinsberg, who expressed his views in 1899. The attempt was made to prove, by embryologic studies, that the tumors arose from invagination of buccal epithelium, with the inclusion of mesoblastic tissue connected with the mandible arches. These facts have made acceptable the dual origin of the tumors, namely, ectodermal and mesodermal, with wide variations due to the degrees of predominance of one of the groups.

The greatest evidence rests with the proponents of the epithelial origin. On the basis of extensive study, Krompecher concluded that these mixed tumors are epithelial in origin.[2] He found that the epithelial cells split off, fibrillate and take on the shape of mucoid or embryonal connective tissue. It has not been determined whether the epithelium is derived from the salivary glands. This theory is tenable for established growths, but some of the early growths exhibit no relationship to the ducts or acini. This apparent defect in an otherwise sound theory may be corrected by the utilization of the branchial origin without disturbing the regular laws of the histogenesis of tumors. Although the epithelial theory is generally accepted in this country, it is not universally approved.[3]

INCIDENCE

Mixed tumors of the salivary glands occur at all ages, although they are found most often in the fourth decade. Of the twenty-four cases reviewed, twelve occurred during this period, and six occurred during

2. Greenberg, H.: Thirty Cases of Mixed Tumors of the Salivary Glands, Arch. Clin. Cancer Research **4**:141 (Jan.) 1929.

3. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1927.

the fifth decade. The youngest patient was 26 years old, and the oldest was 76. There was an equal number of males and females. The parotid was the gland most often affected. The submaxillary gland was involved in only three instances, and no tumor of the sublingual gland was encountered. The majority of the cases were in middle-aged patients, probably because at this period the tumor takes on activity after quiescence of from two to twenty years, and this rapid growth causes the patient to consult a physician. At this stage there is definite evidence of change from a benign growth to a rapidly growing malignant process.

PATHOLOGY

Pathologically, these tumors should be divided into two main groups: first, those seen early, in which there is a predominance of the mesoblastic tissue, and, second, those which are more cellular. In the former group the tumor has been present for a long period and is extremely firm; it is usually flattened and fixed to the substance of the gland itself, although it is sharply outlined and movable. Occasionally these tumors are irregular in shape, and they are often nodular, but most of them are characterized by regularity and apparent innocence, until some outside disturbance causes increased activity. A thick fibrous capsule surrounds the tumor, the weakest part of which is usually located nearest the normal glandular tissue. On section there are whitish-yellow strands of pale glistening, translucent mxyomatous tissue. Between these bundles a softer and more elastic tissue is seen. Differentiated cartilaginous tissue is rarely found on gross examination, but microscopically it is often seen. Histologically, in the first group there are cords of polyhedral dark hyperchromatic cells which occupy the region between the strands of thick hyalinized fibrous stroma. When the cartilage is present it appears as small sheets which occupy an acellular region. Occasionally there is an attempt to form palisades by piling up of the cells.

In the second pathologic class, the growth is also encapsulated, but is much softer than in the former group. The tumor either appears to be a part of the salivary gland or is separated from it by a fibrous capsule. These tumors are representative of the epithelial predominance which is noted after opening the capsule in that there is a diminution of fibroblastic stroma. The substance of the mass is extremely friable and sometimes necrotic. Microscopic examination shows large groups of dark hyperchromatic cells, which are more uniform in size and shape than in the first group. The number of mitoses present depends on the activity of the tumor. In sections small strands of densely organized fibrous tissue are seen surrounding the cells. There may be attempts at gland formation. Occasionally the acini are perfectly shaped and surrounded by thick plaques of fibrous or chondral tissue. However,

the acini that do occur are immaturely formed and are usually located nearest the normal glandular tissue.

CLINICAL COURSE

The course of mixed cell tumors of the salivary glands is usually characteristic. As a rule, the history is that the tumor was noticed first as a small pea-shaped swelling in the region of the gland, which was given no consideration, because there was no pain or variation in size. The onset is frequently thought to occur following septic parotitis or trauma, although this relationship is probably coincidental. After many years of remaining dormant, there is increased activity, which varies with the type of cell and in which trauma may be an exciting factor. If the tumor is removed at this time, it is usually found to be benign, both grossly and histologically. When removal has been incomplete, as is frequently the case, there is usually a recurrence within from a few months to two years. Growth is more rapid than that of the original tumor. The adjacent cervical lymph nodes are not involved unless the tumor is primarily malignant.

There are few conditions from which these tumors must be differentiated. Various lymphoblastomas that involve the nodes nearest the salivary glands probably offer the most trouble. Frequently a definite diagnosis is not made until the tissue has been examined microscopically. A large calculus in the duct of the parotid, with a chronically inflamed gland, caused confusion in one instance. The diagnosis was evident when a roentgenogram was taken, which should always be done if there is an unusual history, particularly in the presence of marked pain. Pain is absent except in cases in which the sensory nerves are involved. Sebaceous cysts must be considered, especially when the lesions are smooth and ovoid and have been present for a long period. Growths which have undergone cystic changes cause the greatest difficulty, whereas typical tumors are less confusing. Removal is often required before a diagnosis is made, although it is best to consider all such growths of glandular origin until they have been proved otherwise.

TREATMENT

During recent years there has been a widespread use of radium and roentgen rays, but the results in our cases do not support their use alone.[4] The opinion of the physicians at the Steiner Clinic is similar to that of Sistrunk,[5] who believed that surgical removal gives the best results.

4. Merritt, E. A.: Mixed Tumors of the Parotid Glands, Am. J. Roentgenol. **25**:507 (April) 1931.

5. Sistrunk, quoted by Patey, D. H.: The Mixed Tumors of the Salivary Glands, Brit. J. Surg. **18**:241 (Oct.) 1930.

Certain tumors show radiosensitivity, and it is these which have a predominance of cellular elements. As a rule, complete regression of the tumor following irradiation is unusual. It is probably beneficial to precede operative removal with a complete course of high voltage roentgen therapy, both for its therapeutic effect and for its value as an indicator of cellular activity.

Thus, the main therapeutic measure must be complete extirpation of the tumor. In an effort to prevent injury to the facial nerve and the soft structures there is always the danger of failure to remove all the diseased tissue. Although it is well in some instances to attempt to preserve the nerve, it must be remembered that only by total removal of the tumor can a permanent cure be effected. Since the facial nerve passes through the parotid gland, it is evident that it would be injured in complete excision of the gland. If the main branch of the facial nerve is severed at the time of the operation, there is a possibility of anastomosing the cut end of the nerve to the spinal accessory or hypoglossal nerve and, by reeducation of the patient, establishing a sufficient nerve supply to the muscles of the face. The inconvenience of peripheral facial nerve paralysis is offset by the knowledge that the tumor has been completely removed.

In several of our cases implantations of radium seeds were made at the time of the operation and high voltage roentgen therapy was used later. This was done in cases in which there had been a previous recurrence and in which it was thought to be impossible to remove the remaining tissue completely without damage to the deep structures. The results of such a procedure have been encouraging, particularly when the tumors were definitely malignant.

COMMENT

The inconspicuous onset and apparent innocence of the growth cause the patient to delay in seeking treatment. The earliest tumor seen in this series had been present only seven months. Twenty years was the longest period before treatment, the average period being between seven and twelve years. It is readily seen that if treatment is given early there is a greater opportunity of completely effecting a cure before the tumor becomes malignant.

Twenty-one cases were of the mixed cell variety, of which eleven were definitely benign. The remaining ten showed evidence of low grade carcinomatous changes. Three cases in the series showed adenocarcinoma of the salivary gland, which is not a high incidence of primary malignancy in this organ. Whereas, in several instances malignant changes were present along with those of the mixed type, it is well to assume that the original lesion was benign. This fact was verified by the clinical course of the tumors.

A combination of surgical removal with the use of roentgen therapy and radium prevented recurrences in only seven cases. There was recurrence of the growth in ten cases. Twelve patients are still living, although there have been recurrences in several. In seven instances the result is unknown. Five patients are known to have died within from a few months to three years after being treated. From these facts it is evident that the prognosis is not good, as the possibility of reappearance of the lesion is very great, recurrence having taken place in more than two thirds of the cases studied. The primary growth should first be completely removed; by this means only can recurrences be prevented. However, when there is a recurrence, it must be treated more actively than the original tumor, because with each recurrence there is a tendency for the growth to become more active, thereby making permanent cure less likely.

REPORT OF CASES

CASE 1.—Mrs. R. E. B., aged 28, was admitted to the Steiner Clinic on Sept. 29, 1930, with a small nodule at the angle of the jaw on the right side, which was first noticed eight years before. The swelling had been gradual, and the growth measured 5 by 5 by 4 cm. The mass was firm and only slightly movable. On October 25, an encapsulated tumor was removed.

Pathologic examination showed that one portion was firm, white and nodular. The remainder was soft and vascular. There was no gritting on cutting. Sections showed an edematous, mucoid structure, with large vacuolated areas surrounded by small hyperchromatic cells. No true glands were seen. These areas were surrounded by dense connective tissue. In other portions large hyaline bundles were found, with small hyperchromatic cells alongside. No cartilage or bone formation was seen.

The diagnosis was mixed tumor.

CASE 2.—Mrs. R. D. C., aged 44, was admitted on Oct. 4, 1929, to the Steiner Clinic, with a tumor mass in the region of the left parotid, which had been present since 1922. Growth had been gradual but steady until 1924, when both roentgen rays and radium were used elsewhere. A period of quiescence followed this treatment, but there was no diminution in the size of the tumor. A symmetrical cone-shaped tumor mass was seen extending in front, below and behind the lobe of the left ear; it measured 4.5 by 4 cm. The skin over the mass showed marked effects of irradiation, with scattered areas of telangiectasia. On October 8 the tumor was removed. In the center gold tubes of radium were found, which had been inserted elsewhere.

Pathologic examination showed an extremely friable and edematous tissue mass, measuring 5 cm. in diameter. There was a very cellular structure composed of medium-sized and small polyhedral cells lying in an edematous fibrous hyaline or myxomatous matrix. The cells showed a clear cytoplasm and degenerated hyperchromatic nuclei. There was no cartilage formation.

The diagnosis was mixed tumor.

On Aug. 15, 1930, about ten months after the operation, there was a firm area 2 by 1 by 1 cm. in front of the scar just under the ear. On Sept. 18, 1931, the patient was operated on again; gold tubes of radium were inserted, and 1,808 millicurie hours of exposure were given. Following the treatment there was a

marked reaction to irradiation and an ulceration developed which required one year for healing. There was no evidence of disease on Jan. 18, 1933.

CASE 3.—Miss L. H., aged 55, was admitted to the Steiner Clinic on July 5, 1929. Two years before, a small lump was noticed in front of the left ear at the angle of the jaw. Growth was progressive until April, 1929, when the mass was opened by her physician, and a small quantity of bloody material was removed. On admission the mass was elongated and firm but not hard, and measured about 2 by 0.5 cm. It was located just below the lobe of the left ear. The tumor was removed with much difficulty on July 13. A portion of the facial nerve was severed.

The tumor mass measured 2 cm. in diameter and was soft and translucent. Sections showed large areas of myxomatous structure together with small areas of beginning cartilage formation. Scattered throughout were clumps of small hyperchromatic epithelial cells without gland formation. One point showed a small area of parotid acini.

The diagnosis was mixed tumor, with a tendency toward malignancy.

CASE 4.—Mrs. C. E. R., aged 56, was admitted to the Steiner Clinic on June 29, 1932, with a small, freely movable tumor mass behind the right ramus of the mandible beneath the ear and attached to the underlying structures. This mass was noticed in 1928, at which time the patient had Vincent's angina. On July 5 the tumor was removed.

Pathologic examination revealed an encapsulated tumor mass 4 cm. in diameter, rounded, slightly lobulated and cystic. The color was reddish blue. A cross-section showed cystic areas with a mucoid secretion. There was an acellular stroma, rather loose and edematous, in which were small collections of hyperchromatic epithelium. No diffuse cellular areas were seen. Large areas were composed of myxomatous structure. In a few areas definite gland formation was present.

The diagnosis was mixed tumor of low grade malignancy.

CASE 5.—A. C., aged 75, was admitted to the Steiner Clinic on June 14, 1929, with a small tumor at the ramus of the left mandible which had been present for twenty years. There had been no appreciable variation in size. The mass was freely movable and firm and measured 4 by 4 by 3 cm. On June 21 the tumor was removed.

Pathologic examination showed a multiloculated cystic mass 3 cm. in diameter with some mucoid areas. There were masses of hyaline connective tissue with scattered areas of sheets and strands of hyperchromatic polyhedral epithelial cells, and some edematous and myxomatous areas, but no cartilage or gland formation.

The diagnosis was mixed tumor.

CASE 6.—W. H., aged 47, was admitted to the Steiner Clinic on Feb. 2, 1931, with a hard mass about 3 cm. in diameter in front of the right ear. There were also several firm nodes in the submaxillary triangle of the neck. The entire tumor mass was removed and a dissection of the glands of the neck was done on February 11. Nineteen gold tubes of radium of 12 millicuries were implanted at the time of operation.

Pathologic examination showed abundant mucoid material but no calcification or cartilage. Sections showed broad sheets of medium-sized and small cells, acidophilic in reaction. There were an abundant hyaline stroma in broad bands and an excessive amount of basophilic mucoid material. Mitoses were scanty.

The diagnosis was mixed tumor.

On April 24 there was no evidence of disease.

CASE 7.—H. H. P., aged 42, was admitted to the Steiner Clinic on May 17, 1929. He stated that twenty-two years before a small tumor was noticed in front of the right ear, which grew very slowly for eight years to about 1 cm. in diameter. In 1917 the mass was removed, only to recur soon afterward. Just behind a curved ¾ inch (1.9 cm.) scar in front of the right ear were four flattened, firm, smooth tumors, which were freely movable and not tender. On May 20 the nodular tissue with mucoid material was removed.

Sections showed a varied structure containing islands of small polyhedral hyperchromatic epithelial cells in irregular arrangement, lying in a hyaline matrix of basophilic mucoid stroma. Other portions showed epithelium lining small glandular cavities.

The diagnosis was mixed tumor of the parotid.

On May 27 and 30 and June 4 a course of roentgen therapy was given.

CASE 8.—H. E. P., aged 32, was admitted to the Steiner Clinic on Feb. 16, 1929, with a tumor in the left side of the face, which had been present for twelve years. This had grown very slowly until five years before examination, at which time the patient was given roentgen therapy. The swelling was reduced materially for about one year, and then the tumor began to grow more rapidly. It was removed by the patient's physician on Jan. 20, 1929.

Pathologic examination showed a large number of strands of small epithelial cells, which were slightly hyperchromatic. The bulk of the tumor was made up of hyaline acellular tissue appearing in bundles supporting the epithelial cells. There was no evidence of gland formation, cartilage or myxomatous structures.

The diagnosis was tumor of the parotid, basal cell carcinoma with hyaline stroma.

The tumor promptly recurred and was again removed; sections showed mixed tumor approaching malignancy. There was a second recurrence, after which the tumor was removed on about Dec. 6, 1932, by the patient's physician. At this time the sections showed masses of scar tissue, with hyperchromatic polyhedral epithelial cells arranged in rounded masses. The central portion was loose and was filled with a basophilic faintly granular material. There was considerable hyaline stroma. The patient has had four courses of roentgen therapy.

CASE 9.—Mrs. L. W. E., aged 47, was admitted to the Steiner Clinic on Sept. 9, 1931, with a swelling in front of the left ear. About six years before the patient had had the mumps, and the left side of the face had been enlarged since. Growth was rapid for four months. About two weeks before her admission to the clinic she went to her physician, who opened the swelling and removed a portion of the tumor. After the operation the swelling increased in size, and a small fistula remained. The mass measured 3 by 4 by 2 cm. It was hard and slightly movable. The patient was advised to have the entire tumor removed, but refused. A biopsy was done, and eight gold tubes of radium were inserted (2,021 millicurie hours). One treatment with roentgen rays was given.

Pathologic examination showed large areas of hyaline cartilage with many epithelial cells. There was no gland formation.

The diagnosis was mixed tumor.

CASE 10.—W. C., aged 38, was admitted to the Steiner Clinic on May 3, 1932, with an enormous mass at the right side of the lower jaw. The swelling had begun twenty years before as a small nodule about the size of a pea at the angle of the jaw. Growth was slow but gradual until just before the patient's admission to the Clinic, when it became more rapid. About March 1, 1932, a small nodule was noticed in the left side of the neck. The mass was elongated, very hard and lobu-

lated and extended from the angle of the jaw downward to the clavicle and in front to the midline. On May 6 the entire mass, which weighed 850 Gm., was removed.

The cut surface showed large areas of necrosis, considerable bone and cartilage. Sections showed large sheets of hyaline cartilage with small areas of myxomatous structure and masses of small acidophilic cells of the salivary gland type. There were also sheets of large hyperchromatic cells, many of which were pavement cells. Mitoses were moderate in number. Scattered areas of necrosis were present.

The diagnosis was mixed tumor of salivary gland origin, radioresistant carcinoma.

On July 24 there was a return of the tumor, and the patient went to another hospital for roentgen therapy. Following this treatment there was no regression, and the patient died six months after the removal of the tumor.

CASE 11.—Mrs. G. D., aged 29, was admitted to the Steiner Clinic on June 30, 1930, with a swelling in the upper part of the left side of the neck. Eleven years before admission, following typhoid fever, the patient had noticed a small node under the angle of the jaw on the left side. The mass gradually enlarged to about 3 cm. in diameter. It was hard, but freely movable. On June 30 the tumor was excised.

Pathologic examination showed an encapsulated tumor 3.5 cm. long and 2 cm. wide. The cut surface was white and firm, with scattered translucent areas. Sections showed poorly formed acini lined with small acidophilic and moderately hyperchromatic epithelial cells. In other areas these cells were in diffuse sheets with myxomatous structure. There were many areas of hyaline cartilage with early calcification.

The diagnosis was mixed tumor, myxochondrocarcinoma.

On Nov. 22, 1932, there was no evidence of disease.

CASE 12.—Mrs. A. V. S., aged 50, was admitted to the Steiner Clinic on Jan. 9, 1930, with a tumor near the angle of the jaw on the right side. Eleven years before a tumor in front of the right ear had been removed; it had been present for many years. The type of this tumor was never ascertained. There was a slow recurrence of the growth in the region of the operative scar. There had been much loss of weight during the previous months. A hard indurated flat mass extended from the angle of the jaw forward to the center of the mandible and upward to just below the zygoma and behind the ear. There was a bluish discoloration on the surface of the skin in the region of the old operative scar. In view of the wide extent of the tumor, operative removal was not attempted, but the growth was treated for two and a half years with roentgen rays at regular intervals, with marked changes. No biopsy specimen was obtained. On Dec. 9, 1932, there was no evidence of disease.

CASE 13.—Mrs. N. G., aged 60, was admitted to the Steiner Clinic on Aug. 4, 1932, with a mass in the left side of the neck just under the chin, which had been present for a year. Growth had been very slow. The tumor was slightly tender and measured 4 cm. in diameter. On August 25 the mass was removed, and radium implants were placed in the neck.

Pathologic sections showed abundant acellular connective tissue with considerable calcification. There were a few scattered areas of medium-sized and small moderately hyperchromatic epithelial cells, with an occasional mitosis. One area showed mucoid degeneration.

The diagnosis was mixed tumor of salivary gland origin, radioresistant carcinoma of low grade malignancy.

The patient was readmitted to the Clinic on October 10 and died on October 13. Autopsy revealed metastatic carcinoma of the liver and chronic nephritis.

CASE 14.—Mr. E. H., aged 56, was admitted to the Steiner Clinic on Aug. 4, 1932, with a swelling of the left side of the face. About a year before he had had a tooth pulled, and immediately after this a lump was noted in the left side of the face. This grew very slowly and became somewhat painful. Various ointments and poultices were applied until the swelling became ulcerated. There was a hard mass beneath the left ear, extending down in the neck for about 1 inch (2.5 cm.). An ulceration was in the center of the mass about ½ inch (1.2 cm.) in diameter. There was facial paralysis.

Biopsy showed extensive necrosis, with abundant dense connective tissue in which were many strands of medium-sized hyperchromatic epithelial cells without acini formation. There was an occasional mitotic figure.

The diagnosis was radioresistant carcinoma simplex.

CASE 15.—J. E. McI., aged 47, was admitted to the Steiner Clinic on April 2, 1929, with a swelling on the right side of the face. This was first noticed seventeen years before when he had received a blow on the face. It remained stationary until eighteen months previous to admission when it began to grow and cause pain on eating. Just in front of the right ear was a hard tumor 3.5 cm. in diameter. It was fixed on movement of the jaw. On April 5 a partially encapsulated tumor was removed. There was an abundant fibrous stroma in which were large islands of medium-sized hyperchromatic cells showing occasional mitoses. The connective tissue was acellular. Section of two lymph nodes showed them to be the seat of metastases.

The diagnosis was carcinoma of the parotid, with metastases to lymph nodes.

CASE 16.—J. R. R., aged 43, was admitted to the Steiner Clinic on March 12, 1928, with pain in the left side of the jaw. Four years before he had been operated on for a thickening in front of the ear. No definite tumor was found, and no tissue was removed. There had been marked pain and fulness in the region of the left ear. At the angle of the jaw, just in front of the mastoid process, a tumor was felt, which was firm and apparently arose deep within the neck and extended well forward. On March 30 the tumor was exposed, but could not be removed, owing to the depth and extension. A biopsy specimen was taken, which showed masses of connective tissue in which large alveoli were filled with small hyperchromatic cells arranged around a large lumen filled with mucoid material.

The diagnosis was adenoma-carcinoma of salivary gland origin.

The patient received several courses of roentgen therapy, with no benefit. Death occurred in 1931. Autopsy showed metastases to the pleura.

CASE 17.—G. B., aged 23, was admitted to the Steiner Clinic on May 27, 1925, with a lump in the left side of the face. The tumor had been present for twelve years. It grew very slowly for two years, after which it was removed by the patient's physician. A few months later it was noticed that the tumor was recurring. At the lower pole of the left parotid a smooth, firm, globular, movable tumor was found, which measured 3 cm. in diameter. The skin was adherent to the tumor. Two small nodules were felt below this main mass. Preoperative irradiation was given, and on June 12 the tumor was removed.

Pathologic examination showed dense tissue, which cut with some difficulty and showed mucoid material with large areas of hyaline cartilage and small areas of glandular structure.

The diagnosis was mixed tumor of the parotid.

There was no evidence of the disease when the patient was last seen.

CASE 18.—R. B. R., aged 44, was admitted to the Steiner Clinic on June 6, 1925, with a tumor in the left side of the face, which had been present for ten years. Two years before admission the tumor began to enlarge and cause considerable pain. Roentgen therapy was given, with some retardation of the growth. Immediately below the left ear between the angle of the jaw and the mastoid process was a hard, smooth, fixed, flat tumor mass measuring 4 by 3 cm. In the posterior triangle of the neck were firm fixed lymph nodes, from 0.5 to 2 cm. in diameter. Two radium treatments in the form of a pack were applied to the upper and lower tumors. On June 20 a node was removed; this showed dense masses of connective tissue with many tumor cells. The cells were large, with hyperchromatic nuclei, and were fused. There were other areas of polyhedral cells with hyperchromatic nuclei.

The diagnosis was carcinoma of the parotid.

The patient died on December 6.

CASE 19.—Mrs. F. M. L., aged 54, was admitted to the Steiner Clinic on Aug. 6, 1926, with a large tumor in the region of the left parotid gland. On July 21

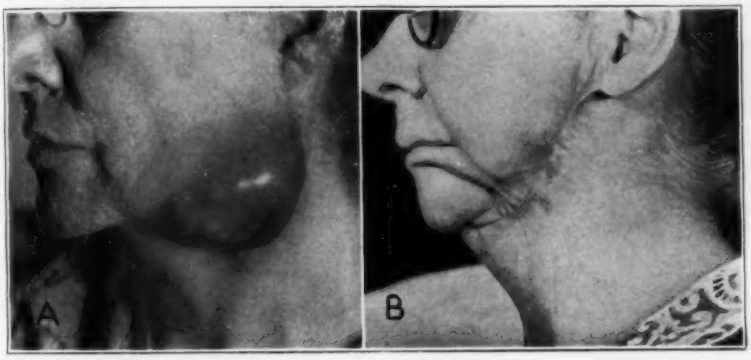

Fig. 1 (case 19).—*A*, photograph of patient taken in 1926, showing primary tumor of the parotid; *B*, photograph of patient taken in 1930, after secondary operation of resection of the mandible followed by a bone graft.

an encapsulated tumor was removed, which measured 9 by 6 by 4 cm. Sections showed diffuse sheets of rounded cells with a fairly clear cytoplasm and a well marked nucleus and nucleolus. There was much hyaline material, into which the cells gradually merged. Other areas showed diffuse growths of epithelium of small rounded and polyhedral cells with hyperchromatic nuclei, forming atypical glands and ducts.

The diagnosis was mixed tumor of the parotid, adenocarcinoma.

On July 8, 1929, recurrence was noted, and a biopsy section was taken to confirm this fact. Gold tubes of radium were placed in the tumor. On Dec. 16, 1929, roentgen therapy was begun. On Jan. 10, 1930, roentgenograms showed destruction of the left side of the mandible. Resection of the left side of the mandible was done, which showed metastases to the mandible. Dissection of the neck was done on Feb. 14, 1931, after there was a recurrence of growth in the anterior chain of the cervical lymph nodes. On November 20 a bone graft was placed in the defect in the mandible. On March 28, 1932, metastases were noted in the left occipitoparietal region of the skull. Four months later there was no

increase in the size of the metastases. The patient had six complete courses of roentgen therapy, including treatment of the process in the supraclavicular nodes and the skull, from 1926 to the time of admission. Gold tubes of radium were inserted in the nodes and recurrent growths on three occasions. On Jan. 9, 1933, the patient was living and doing nicely; there was no further evidence of recurrences.

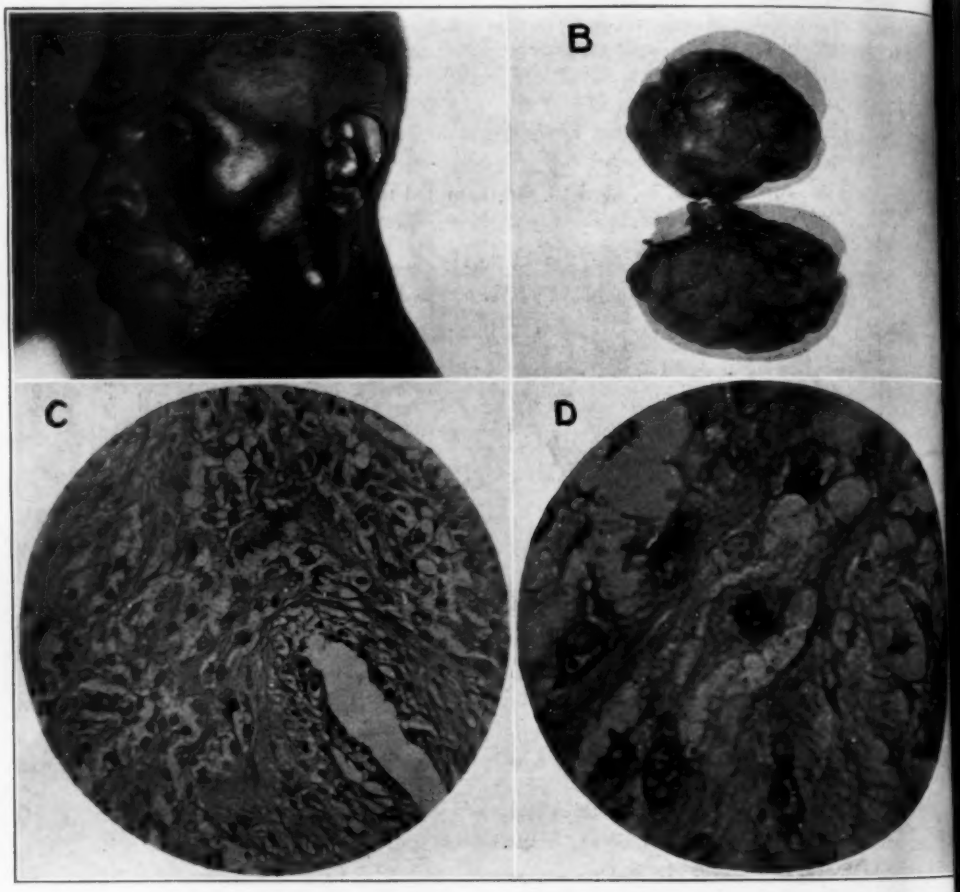

Fig. 2 (case 20).—*A*, photograph of patient, showing carcinoma of left parotid gland; *B*, gross appearance of tumor removed at first operation; *C*, low power magnification, showing cellular character of the growth; *D*, high power magnification, demonstrating mitosis.

Case 20.—T. C. E., aged 49, was admitted to the Grady Memorial Hospital on Aug. 3, 1932, with a tumor in the left side of the face, which had been present for twenty years. It had been about 1 cm. in diameter until about eight months before admission, when it began to grow and cause some pain. An ovoid tumor mass measuring 3 cm. in diameter was felt at the angle of the jaw. It was firm

and fixed to the surrounding structures. The tumor was removed, along with a portion of normal parotid tissue, without injury to the facial nerve.

Sections of the tumor showed numerous epithelial cells, which were surrounded by dense strands of connective tissue. There were numerous mitoses in the epithelial cells, and many polymorphonuclear leukocytes were present.

The diagnosis was carcinoma simplex.

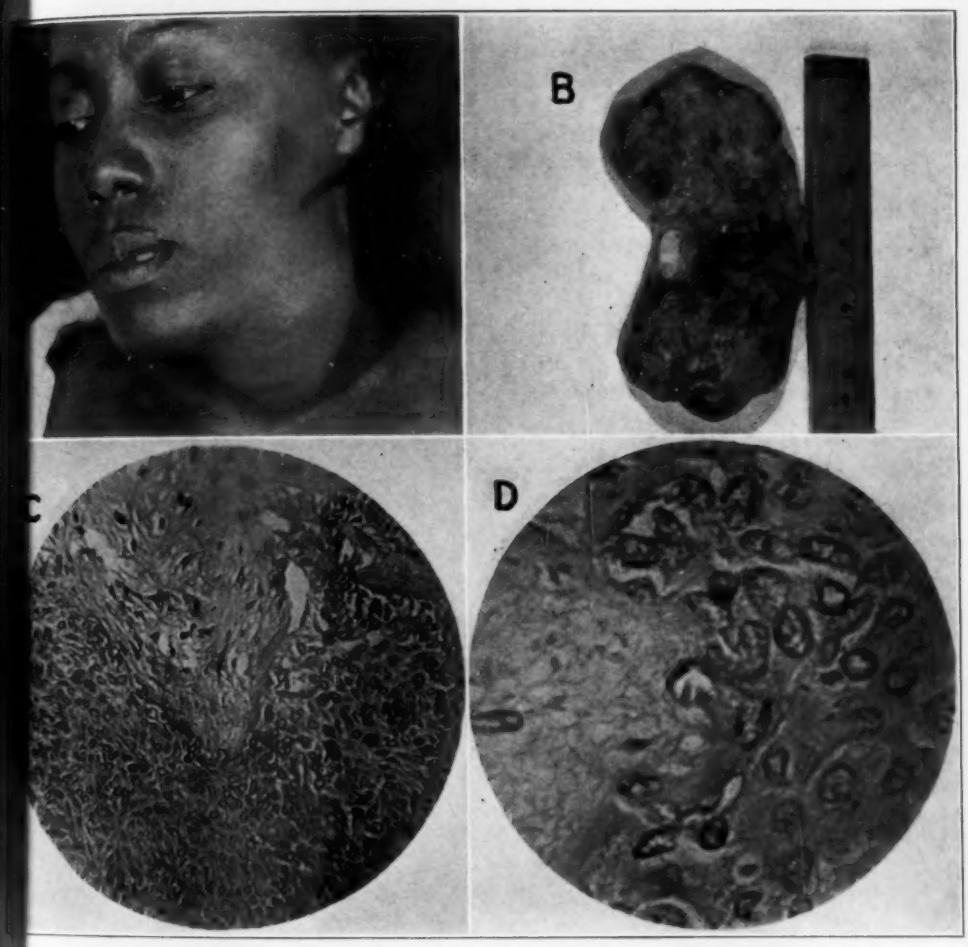

Fig. 3 (case 21).—*A*, photograph of patient, showing mixed tumor of the left submaxillary gland; *B*, gross appearance of cross-section of tumor; *C*, low power magnification, demonstrating the two types of tissue; *D*, magnification showing character of cells.

On Jan. 28, 1933, there was a recurrence of the tumor to twice the size before the first removal. A complete course of roentgen therapy was given, without regression. The entire parotid was removed on March 10, and radium was implanted in the wound (2,000 millicurie hours).

Sections of the recurrent tumor showed a very active carcinoma of the parotid gland.

CASE 21.—M. J. was admitted to the Grady Memorial Hospital on Feb. 27, 1932, with a tumor in the left side of the neck. The swelling was noticed seven years before admission after an attack of sore throat. Growth had been slow but progressive. The tumor was felt under the lower border of the mandible; it was freely movable but firm. On February 28 the mass was removed and was found to be encapsulated. It measured 6 by 5 by 4 cm.

On cut section the tumor was firm and had a hard gritty feeling. Microscopic examination showed immature alveoli. There were many hyperchomatic cells, which were regular in size. There were large bands of acellular fibrous stroma, with scattered areas of cartilage.

The diagnosis was mixed tumor of the salivary gland.

Fig. 4 (case 23).—Appearance of typical tumor under low power magnification.

CASE 22.—L. K., aged 56, was admitted to the Grady Memorial Hospital on Oct. 10, 1931, with a tumor mass in front of the left ear, which had been present since February. Growth had been rapid during recent months. Examination showed a firm tumor about 2 cm. in diameter just in front of the left ear. The tissue was grayish yellow and quite firm. Sections showed an extremely cellular tissue, with a small amount of stroma. The cells contained many mitotic figures. There were areas that contained a compact hyalinized cellular tissue.

The diagnosis was carcinoma of the parotid.

The tumor recurred within a few months and was treated with radium at the Steiner Clinic.

CASE 23.—C. W., aged 44, was admitted to the Grady Memorial Hospital with a tumor in the region of the right parotid. The swelling had first been noticed two years before and had grown gradually since. The mass was firm and ovoid in shape, occupying the region of the right parotid gland. It was well encapsulated and measured 6 cm. in diameter. There was much firm, cartilaginous tissue scat-

tered throughout. Many hyperchromatic cells were located between the strands of fibrous connective tissue.

CASE 24.—M. F., aged 45, was admitted to the Grady Memorial Hospital in September, 1932, with a tumor mass in the left submaxillary region, which had been present for two years. The tumor was well encapsulated, freely movable and not tender. It measured 6 by 5 by 4 cm. On section the center was found to be extremely necrotic and friable.

Pathologic examination showed many large hyperchromatic cells surrounded by strands of dense fibrous connective tissues. Mitoses were present.

The diagnosis was mixed tumor with early malignancy.

SUMMARY

1. The so-called mixed tumors constitute the largest number of growths of the salivary glands.

2. The most widely accepted theory of the formation of mixed cell tumors of the salivary glands is that of an epithelial origin, although there is still some difference of opinion concerning their exact nature and formation.

3. Pathologically, these tumors may be grossly divided into two classes, depending on the predominance of the embryonal tissue. The more cellular the tumor, the more likely is recurrence when the growth has not been completely removed.

4. The use of roentgen rays and radium and early removal of the primary growth offer the greatest hope for cure.

5. The prognosis, based on a study of the treatment in twenty-four cases of tumor of salivary gland origin, is not good either for complete cure or for prevention of recurrence.

6. Following the removal of the original tumor, the recurrent growth becomes more malignant.

EXPERIMENTAL BONE TRANSPLANTATION

WITH SPECIAL REFERENCE TO THE EFFECT OF "DECALCIFICATION"

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AND
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In recent years, many of the old, well established concepts of the physiology of bone have been profoundly altered in order to become adapted to the newer beliefs. No longer is each histologic division of adult bone singled out by some one group of investigators as the sole bone-forming element. The belief is growing that the processes of osteogenesis, regeneration of bone and healing of bony defects are far more complicated than was previously thought. It is being recognized that these biologic manifestations are dependent on intricate biochemical or "humoral" phenomena with which investigators are but slightly familiar. As Leriche and Policard (1928) pointed out: "The problem of osteogenesis has passed through many phases. It has been histological and surgical and at the present time it is above all chemical. . . . It is now the turn of the chemists and physicists. They alone can open up new horizons by giving us some of the certainties which we lack."

CURRENT VIEWS ON FORMATION, CALCIFICATION AND DECALCIFICATION OF BONE

The authors just quoted, who are among the most thorough of modern workers, have elaborated the theory that all formation of bone is the result of metaplastic change in the connective tissue where bone is to be laid down. This metaplasia, they stated, takes place in three stages: (1) transformation of connective tissue by edematous infiltration, with multiplication of connective tissue fibrils; (2) infiltration by a special substance, clinically undefined, the preosseous substance; (3) deposits in that substance of a mixture of calcium phosphate and calcium carbonate, producing bone. Moreover, all formation of new bone at the sites of healing is accompanied by resorption of preexisting bone, and in fact depends on it, for as a result of the

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rarefaction of bone, there is produced a localized oversupply of calcium which stimulates osseous metaplasia. This resorption of bone is accomplished by alterations in the local circulatory activity, which these investigators think is regulated by some humoral phenomenon.

Since 1923, Robison and his co-workers at the Lister Institute in London have amassed a wealth of evidence to strengthen the assumption that at least in the ossification of cartilage of young animals an enzyme ("bone phosphatase") is essential. The substance has been found to be very active in hydrolyzing the phosphoric esters of the blood corpuscles and plasma to release free phosphoric acid at the site of formation of bone. Thus, calcification is aided by enzymatic activity, and "the production of the enzyme is a part of the cellular activities which result in the formation of bone."

Keith proposed that there is an intimate relationship between vascular tissue and production of bone. He expressed the belief that formation of bone is engendered by the presence of a substance, or tissue, which stimulates the neighboring capillary system to throw out processes to bring about absorption in the body. In the invading vascular buds are cells (derived from the capillaries or from reticulo-endothelium) which may become osteoblastic or osteoclastic in their action. Keith stated also that he considers it essential that there be present a supply of suitable calcium salts in solution, and possibly some enzyme.

In each of these modern theories of growth of bone emphasis is placed on two basic beliefs: (1) that the calcium of the skeletal system is not a fixed, stable framework as much as it is a very accessible source of calcium to the blood stream, and (2) that all the phenomena of regeneration of bone are intimately dependent on vascular changes.

Relation Between Circulation and Calcification.—As early as 1908, Patterson pointed out that apart from their function as a supportive skeleton the bones were without doubt reservoirs of calcium. He expressed the belief that they acted as storers of calcium and that calcium could be lost, relative to the other salts, by selective autolysis. In 1929, Bauer, Aub and Albright reported that the trabeculae of cancellous bone served as a readily available supply of calcium and also that the trabeculae were more rapidly affected at the more vascular extremities of the long bones. In other words, the physiologic and even the morphologic characteristics of bone have been found to be closely bound up with the variations in its blood supply and with the fluctuating demands of the organism for "labile" calcium.

There is, furthermore, considerable clinical and experimental evidence to support the belief that atrophy or decalcification of bone is accompanied by an increased blood supply. And it is believed that alterations of the content of calcium (and of the vascularity) of the

skeleton produce definite changes in the rate of healing of bone. In our present work, we shall consider the effects of decalcification of animals, with the resultant increased vascularity of bone, on the healing of experimental bone transplants.

Decalcification and Atrophy.—Nearly sixty years ago, Förster first made the observation that with insufficient calcium in the food the muscles lost 60 per cent of their content of calcium and there was also considerable diminution in the calcium content of the bones. Shortly afterward, Voit discovered that the bones of an animal on a calcium-poor diet were more brittle than those of a normal animal, that the skeleton had a smaller dry weight and that the quantity of calcium in all the organs of the body was more or less diminished. Leriche and Policard recently stated that "in compact bone, enlargement of the haversian canals is the dominant sign of bone absorption" and that "this is always accompanied by circulatory increase." In such a process, the cellular structure is preserved and "the calcium phosphocarbonate disappears, like the glycogen of the hepatic cell or the fat of the adipose cell."

Jaffe has emphasized that resorption of bone is much more of a vascular and chemical phenomenon than an osteoclastic one. He stated that when there is a negative calcium balance the bone in the vicinity of the vascular canals becomes decalcified and the vascularity is increased. On the other hand, Radasch demonstrated that the atrophy of senile bone is primarily an osteoclastic phenomenon involving erosion of the cortex from the medullary cavity. This type of decalcification is distinct from and dissimilar to the vascular erosion which we are discussing.

With these considerations in mind, we became interested in the interrelations of atrophy, decalcification and the healing of bone. We attempted to determine whether when animals were decalcified by being given food low in calcium, distilled water and ammonium chloride the increased vascularity of the bones would lead to more rapid healing of bone. In other words, we wondered whether the healing of bone could be hastened if the bone were made more vascular and osteoporotic. Such a change is obviously a chemical one, widespread enough to cause a definite change in the process of ossification and formation of new bone.

This idea came about through the association, several years ago, of one of us (Ghormley) with Aub and Bauer, in the Massachusetts General Hospital. These workers were making some studies on the calcium balance, and Ghormley had a patient with scoliosis whom he wished to prepare for surgical intervention by stretching in a recumbent position over a period of several weeks. Aub and Bauer agreed to keep the patient in one of the beds of their service while the process of

stretching went on. At the same time, for their own study they kept the patient on a diet that produced a negative calcium balance. At the time of operation a decided decrease in the density of the bone was noted. The bone could be chiseled easily without the use of a mallet. After operation, when the patient was restored to a normal diet, rapid fusion at the site of operation on the spine took place. So rapid and satisfactory was the fusion that we have always thought that the "decalcification" previous to the operation had something to do with the result obtained.

REVIEW OF THE LITERATURE

The literature on growth, regeneration and repair of bone has been surveyed often, and although these controversial matters have been frequently studied, we feel that it is a distinct contribution to assemble in outline all the available bibliographic material related to these subjects. In presenting this extensive summary of the literature, we make no claims to originality for the classification, because we have followed in part the outline utilized by Bull.

The theories of growth and regeneration of bone can be classified in five groups, each view being exemplified by the statement of an outstanding exponent: 1. Ollier (1867) maintained that growth and replacement of bone are due to specific osteogenic activity of the osteoblasts of the periosteum. 2. Barth (1893) said that all transplanted bone dies and is replaced by proliferation of new bone from the surrounding host bone into the dead transplant. The graft is osteoconductive. 3. Axhausen (1908) supported the view that repair of bony defects and the replacement of bone grafts are effected by deposition of bone by the periosteum and the endosteum. 4. Macewen (1912) claimed that bone grows and repairs itself by proliferation of the bone cells. The periosteum serves no osteogenic function and acts merely as a limiting membrane to the growing bone. 5. Baschkirzew and Petrow (1912) wrote that all new bone is formed by metaplasia of the preexisting connective tissue in the region where it is to be laid down.

Each experimental or clinical observation on some phase of physiology of bone we have abstracted and arbitrarily forced under one of these five theories. The obvious paradoxes and contradictions we shall pass without comment, for Groves and others have rationalized the divergent points of view most satisfactorily.

1. *Growth and replacement of bone are brought about by specific osteogenic activity of the periosteum.* Dellamotte (1694) in a case of compound fracture resected subperiosteally 6 inches (15.2 cm.) of a tibial shaft. Eight months later a new shaft had formed.

Duhamel (1742), in studying experimental fractures in animals which had been fed madder, determined that bone was laid down by the deep layers of the peri-

osteum (comparable to the cambium layer of growing wood) and that madder was deposited only in newly formed bone. He found that growth in the length of bones took place at the ends, but he did not study the epiphyses. Periosteum produced bone "as an exogenous stem grows from the inner layer of the bark."

Subperiosteal resection of bones of animals and man convinced Syme (1831) that bony defects were repaired by new bone laid down by the periosteum.

Flourens (1842) performed many experiments which corroborated Duhamel's view that new bone is deposited by the under layers of the periosteum.

Ollier (1867), in experiments on young dogs and other animals, found that transplanted periosteum produces bone, that suppuration does not prevent osteogenesis, that transplanted marrow does not produce new bone, that periosteal flaps or periosteal transplants are fully osteogenic in young animals but not in adults and that the power of osteogenesis, if lost to the adult periosteum, can be revived by stimulation of the compact bone beneath. He noted that if bone is resected without destroying the periosteum new bone forms and that transplanted bone dies when the periosteum alone is grafted.

Cushing (1899), following Nichols' idea, resected subperiosteally a necrotic tibia, closed the periosteum and found later that an entire new shaft was formed by the periosteum.

Grohé and Morpurgo (1899) found that after several hours' preservation outside the body, transplanted periosteum retained its vitality and osteogenic power.

Colvin (1907) performed subperiosteal resection of entire bones for osteomyelitis in several cases and later found that complete regeneration of their shafts had taken place.

Tomita (1908) stated that new growth is from the inner layer of the periosteum and from the marrow cells. The cells of the bone itself have no power to form new bone.

Nakahara and Dilger (1909) found that free transplants of periosteum caused regeneration of bone in a fair proportion of cases.

Zondek (1900), after a study of experimental fractures in mice, attributed an osteogenic function to the periosteum in the formation of callus.

Janeway (1910) reported on bone grafts in man. The implanted bone dies, he said, but is replaced by the periosteum and marrow, which live.

Pochhammer (1911) stated that the periosteum produces cartilage and bone after fracture.

Carrel (1912), working on dogs, found that periosteum transplanted under the skin produced bone.

Trinci (1912) stated that transplanted periosteum is capable of causing early regeneration of bone.

Jokoi (1912) produced new bone in six of ten cases by injecting beneath the skin or into the muscles an emulsion of periosteum of the tibias of young dogs.

Haas (1913) demonstrated that regeneration of bone is not dependent solely on the presence of preexisting bone. Regeneration of bone was never found, however, except when periosteum was present.

Schepelmann (1913) said that periosteum when transplanted into the omentum, mesentery, liver and other organs caused growth of persistent new bone. It is important, he stated, to preserve vascularity and the integrity of the cell and to use the entire periosteum.

Oechsner (1914) stated that after the placing of bone grafts in defects the periosteum causes regeneration of complete shafts of bone.

Mayer and Wehner (1914), in experiments on animals, found that transplanted periosteum produced new bone. Adult bone cells demonstrated no proliferative ability. "Most of the bone cells of the transplant eventually die," they wrote, "though frequently the graft is revascularized sufficiently early to preserve some of the bone cells. New bone growth is dependent upon activity of the periosteum and the endosteum."

Haas (1914) wrote: "It is apparent that the periosteum is very actively concerned in the regeneration of bone."

McWilliams (1914) stated that in some cases transplanted periosteum produces new bone. The life of the graft is dependent on a sufficient blood supply. Transplantation of periosteum with the bone insures an adequate blood supply.

Todyo (1917), in experiments on dogs, found that many of the components of the graft survived, particularly the periosteal and subperiosteal tissues. "The periosteum will actively form new bone," he wrote.

Berg and Thalhimer (1918) wrote: "Fully developed bone cells, in the accepted sense of the term, that is, cells within well calcified lacunae, have never been shown by microscopic observation to have divided and formed new bone." Other views of these investigators were as follows: The periosteum of a living autogenous graft remains alive after transplantation, and thereby the life of the transplanted bone is maintained. Periosteum devoid of adherent bone cells, when transplanted into foreign tissue, produces bone. Endosteum and osteoblasts lining the haversian canals in bone transplants produce bone very actively. The cambium layer, when adherent to transplanted cortex, produces bone.

Mayer (1919) wrote: "The fully developed bone cell has no power of division and bone growth results from the activity of cells lying between the bone and outer layers of the periosteum."

From a report of Delangenière and Lewin (1920) the following statement is quoted: "One can be certain that a layer of bone, with its periosteum, produces new bone and that this bone gradually grows and replaces lost bone."

Todd (1920) expressed the following belief: "Cancellous tissue (endosteum) is one of the chief agents in regeneration of bone, and, like the cambium layer of the periosteum, should be treated conservatively at operation. Compact bone plays a very minor part in regeneration."

Simon (1922) stated that living autoplastic bone with periosteum is the ideal graft, since the periosteum aids in proliferation and revascularization of new bone.

Kolodny (1923) wrote: "An adequate blood supply of the periosteum is essential for normal union of fractures. The periosteal callus plays a far greater rôle in union of fractures than the endosteal callus."

2. *All of the transplanted bone dies and is replaced by proliferation of new bone from the surrounding host tissue.* Barth (1893), in transplanting bone to trephine holes in the skulls of dogs, found that all the elements of the graft died and were absorbed and that new bone proliferated from the surrounding living bone. The final success in grafting depended largely on intimate contact between the graft and the living vascular bone. The periosteum, cortex and marrow died, and all the bone acted at first like a foreign body. The graft was gradually replaced by new-formed bone from the adjacent bone-producing tissue. This is the process called "creeping replacement." (In 1908, Barth repudiated this idea and came to believe that the periosteum was the necessary element in the life of a graft.)

Marchand (1901) stated that bone is replaced by proliferation into the necrotic substance of young bone cells from the surrounding cortex.

Grekoff and Frangenheim (1901) maintained that the source of newly formed bone is in the osseous matrix of the bed into which the bone is transplanted.

The view of Murphy (1912) was that the transplanted bone forms a scaffold for the haversian vessels from both ends of the living bone to pass over, forming a callus. Transplanted bone is only osteoconductive. It must be in contact with fresh, living bone if proliferation is desired and complete resorption is to be prevented.

Gallie (1914) transplanted bone without periosteum in dogs. The bone grafts died and were revascularized. Dead bone was resorbed and new bone produced by the bone cells, which invaded the grafts along the route of the new vessels.

Brown and Brown (1915) stated that all transplants are ultimately absorbed. The periosteum seems to have little influence on the early establishment of a blood supply.

Ely (1919) wrote: "Three things are necessary for bone formation: 1. Blood vessels. 2. Loose meshed fibrous tissue, a homogeneous matrix of granular or necrotic material. 3. A stimulus, physiological or pathological, as the case may be. . . . It is seen therefore that neither periosteum nor marrow is necessary for bone formation and that neither of them forms bone, in the proper meaning of the word."

Gallie and Robertson (1919) said that when bone is transplanted, the cells on the surface or in the haversian canals may live and proliferate; the remainder die and are absorbed. New bone proliferates on the periosteal and endosteal surfaces of the graft.

Ely (1924) stated that when a piece of bone is transplanted to the soft tissues of an animal, the bone and its marrow die; soon vascularization of the marrow begins, and shortly thereafter, formation of bone.

3. *Replacement of bone grafts and repair of bony defects are effected by proliferation of bone from the periosteum and the endosteum.* Radzimowsky (1891) said that when living, periosteum-covered bone is transplanted, the bone tissue proper dies, but the periosteum lives and produces new bone, which is deposited not only on the surface of the transplanted dead bone but in its lacunae and in the enlarged haversian canals.

Bonome (1885), in studying fractures in rats, found that bone in the immediate vicinity of the fracture died. His belief was that it was resorbed and replaced by new bone which was formed from the osteogenic layer of the periosteum.

Nichols (1904) stated that repair of a bony defect occurs by proliferation of epithelioid cells from the periosteum, accompanied by blood vessels, and by proliferation from the layer of cells lining the inner surface of the cortex (endosteum). The cortical bone seems to have a very limited or no power of proliferation.

Axhausen (1908) performed and reported in detail 146 experiments on animals with many different types of grafts. He wrote: "There is marked cellular proliferation under the periosteum, also the marrow showed proliferation, absorption and production of new bone under the periosteum, by proliferation from the endosteum, and around the new vessels which penetrate the dead bone. . . . The chief source of the young bone which replaces the necrotic bone of the transplant is the periosteum, next in order comes the marrow and endosteum."

Läwen (1908) for removal of a malignant growth resected the upper end of the humerus of a boy, aged 8 years, and replaced it with a graft from the tibia. The arm was amputated eleven weeks later owing to recurrence of the growth. The graft was richly vascular, and bone cells were resorbed. There was marked periosteal and endosteal proliferation, and new bone was forming around the new vessels.

Lobenhoffer (1910) expressed the belief that in a transplant with periosteum the cortical bone dies and is absorbed and the periosteum remains viable and produces new bone.

Albee (1913) wrote: "It is believed that periosteum and marrow substance on the bone graft serve an important rôle in aiding to establish an early and more abundant blood supply from the recipient bone to the transplant. . . . It seems very probable that the amount of haversian blood supply is in a very large degree, if not wholly responsible in determining whether the bone graft lives as such or acts as an osteoconductive scaffold."

Lexer (1908) stated that the bony tissue of a transplant is gradually absorbed and is replaced by bone which is formed from the periosteum chiefly and from the medulla in part, and that the periosteum also aids in cementing the graft to the wound and in stimulating capillary invasion and early nutrition.

McWilliams (1914) expressed himself as follows: "The living graft should be transplanted always with the periosteum on it. This is most important. . . . It seems probable that the influence of the periosteum is exerted in maintaining the nutrition of the graft."

Phemister (1914) wrote: "Osteogenesis in bone repair occurs from the inner layer of the periosteum, from the endosteum, and to a much less extent from bone cells and fibrous contents of the haversian canals." He stated, furthermore, that the viability of a transplant depends on the ability to secure nourishment; therefore, the outer cells survive and proliferate.

McWilliams (1914) again wrote: "The periosteum survives because of its sufficient blood supply from the surrounding tissues. Its inner surface forms osteoblasts which themselves proceed to reform the bone of the graft, in the event that the osteoblasts within this have died from a deficient blood supply."

The following passage is quoted from Albee (1914): "The endosteum, marrow substance and periosteum should be included on the graft, as they play a most important rôle in aiding to establish an early and sufficient blood supply from the recipient tissues to the cortical part of the graft. The endosteum is also actively osteogenetic as well as the inner layer of the true periosteum."

Haas (1914) expressed the following view: "The periosteum is directly and actively concerned in the regeneration of bone. The regeneration of bone also takes place from the marrow but to a more limited degree."

Gill (1915) transplanted entire metatarsal bones in dogs and noted good healing in most cases, with little necrosis of bone. He stated: "Revascularization of a graft takes place early and first reaches the exterior—the most vital portion of the graft."

Brooks (1917) wrote: "The living bone transplanted with the periosteum and endosteum is the only type of implant which has osteogenetic properties. . . . Osteogenesis is from the junction of the periosteum and cortical bone rather than from either alone."

Nathan (1921) expressed his belief as follows: "Bone is produced solely by osteoblasts. The osteoblasts are always confined to the cambium layer of the periosteum or the endosteum. The osteoblasts are also found in the bone marrow." Bone grafts, he said, should include the periosteum and the endosteum.

Albee (1923) said that most of the blood supply to a graft is derived from the marrow and that an early blood supply is essential to the life of a graft.

Klinkerfuss (1924) wrote: "Solid bone grafts in the main die, are absorbed and replaced by new bone tissue resulting from the proliferating of osteoblasts of the periosteum, endosteum and haversian canals."

Haas (1924) stated: "The chief source of osteogenic cells, for the repair of a fracture in a transplanted bone, is from the osteoblasts of the periosteum and the endosteum. The presence of either is sufficient for union. The periosteum plays a relatively more active part than the endosteum."

Rohde (1925) expressed himself as follows: "Cortex denuded of periosteum and marrow and endosteum does not take part in bone formation. . . . Bone-building power is found only in specific bone-building tissues (osteoblasts of the periosteum and marrow endosteum)."

Kartaschew (1930) stated that the periosteum and the endosteum are important in transplanting bone. Small chips of bone permit circulation to reach the haversian canals earlier and aid the endosteal proliferation.

Haldeman (1932) said that the periosteum plays the chief part in the healing of fractures. Endosteal (medullary) callus aids in the healing of fractures but in the absence of periosteum is often unable to complete the union.

4. *The periosteum has no osteogenetic function. Bone grows and repairs itself by proliferation of the bone chips.* Havers (1692) studied the microscopic structure of bone and determined that the periosteum is merely a connective tissue, a limiting membrane which vascularizes the bone.

Macewen (1912) said that the bone cells of the cortex, occupying the lacunae of the bony substance itself, are the active agents in the life and regeneration of a transplant. The periosteum is only a limiting membrane and takes no part in osteogenesis. The periosteum acts merely as a "limiting membrane to the osteoblasts issuing from the interior of the bone. . . . The vegetative capacity of the bone cell is fully as great as that of the epithelial cell." The periosteum is the medium through which the bone gains some of its blood supply, but it is not indispensable. Many cases have been reported in which subperiosteal resections of bone were made and in which there was no replacement by bony tissue. Diaphyseal bone is reproduced by the proliferation of osteoblasts derived from pre-existing osseous tissue. Regeneration takes place independently. "The periosteum plays no part in the reproduction of bone after transplantation."

Geddes (1912) wrote: "Bone derives from the ectoderm and not from mesoderm. Osteoblasts arise from the cells of the ectoderm and migrate as individuals to the sites of bone formation, passing through the periosteum en route. Periosteum, far from being an osteogenetic membrane, is a limiter of bone formation."

McWilliams (1912), in using ribs in experimental transplants, found that the periosteum seemed to hinder the early development of a blood supply. It served no osteogenic function.

Vogt, after subperiosteal resection of the shaft of a humerus, found no evidence of regeneration of bone.

Gallie and Robertson (1914) studied the healing of defects produced in bones of young and old animals. The periosteum, they thought, is merely a fibrous membrane without osteogenic function, and osteogenesis appears to be solely a property of the endosteum and to be as energetic in the absence as in the presence of the periosteum.

Bancroft (1914) made studies on the healing of experimental defects in bone. He wrote: "The periosteum acts as a limiting membrane to bone, tends to conserve its shape and to furnish its blood supply." Small pieces of transplanted bone grow without the aid of periosteum.

Moore and Corbett (1914), in experimental transplantation of bone in animals, found that fascia is a suitable substitute for periosteum. "Periosteum is not an essential element in the healing of bone," they stated.

Cohn (1914) wrote: "We believe that small bony transplants are osteogenetic and not essentially osteoconductive. The periosteum has no osteogenetic function, but is rather a limiting membrane. Periosteum is not essential to the repair of defects in bone."

Lewis (1914), after clinical observations, concluded that gaps in bone are filled by growth from the ends of the divided shaft under periosteal limitation and control.

Groves (1914 and 1917) expressed the belief that the periosteum is the product and not the mother of bone. All the osteogenic properties of the periosteum are due to the more or less accidental presence of the outer layer of bone cells adherent to its deep surface. Living bone is the chief source and origin of callus, which grows mainly from its outer or periosteal surface. The periosteum is chiefly a limiting membrane of the bone. The dense bone can live, grow, undergo repair and produce fresh periosteum after the periosteum has been removed.

Davis and Hunnicutt (1915), after experiments on dogs and rabbits, concluded that periosteum alone (even when osteoblasts are demonstrated) does not produce bone when transplanted. Periosteum with bone shavings attached produces new bone, they said. Particles of bone and accompanying osteoblasts are necessary for the production of bone. Periosteal flaps when attached by pedicle to the bone still do not produce bone. The nourishment of bone is in no way affected by the stripping off of the periosteum. The periosteum acts as a limiting membrane. Growth of bone into defects is from the shaft itself.

Cohn and Mann (1916) stated that the periosteum is a source of added blood supply and a limiting membrane. The endosteum and the cortical osteoblasts lying under the periosteum are the sources of formation of callus. Transplants are usually absorbed.

Dobrowolskaja (1916) cultured, incubated and studied small pieces of bone of animals. There was definite evidence of proliferation from the detached pieces of cortical bone. He expressed the belief that when the bone is transplanted with its periosteum the growth is evidently more active.

5. *New bone is formed by metaplasia of the preexisting connective tissue in the region where it is to be laid down.* Von Haller (1766) wrote: "We cannot yet distinguish the bones themselves of which the first appearance is mucus. . . . Thus the muscles, by their action, draw out the processes from the bone, and dilate the small cavities into large cells; and likewise incurvate the bones and variously modify their shape. . . . The bones at first are soft and of a mucous nature; then they acquire the consistence of jelly; and this afterwards becomes a cartilage, without any change of parts, as far as can be observed. Cartilage however is not so imperceptibly converted into bone. It never happens without the red blood making a passage for itself into the vessels of the bones. Round these vessels are formed cellular texture and laminae, which the vessels themselves seem to compress into a medullary tube. . . . But even a bony callus never becomes sound till newly formed red vessels have penetrated its substance. . . . The periosteum covers the bones as membranes the viscera . . . nor does the periosteum at all adhere to the bone, except in the epiphysis."

Hunter (1786) wrote as follows: "Bones receive most of their nourishment from the surrounding parts, as from the periosteum. . . . Bones grow by two processes going on at the same time and assisting each other; the arteries bring the supplies to the bone for its increase; the absorbents at the same time are employed in removing portions of the old bone, so as to give to the new proper form."

Blessig (1859) observed calcification of the kidneys of rabbits killed from four to six days after ligation of the left renal artery.

Paul (1886) stated that senile degeneration of arteries presents three steps: (1) calcareous degeneration; (2) irritation about these plates from fracture or other injury, leading to inflammatory proliferation; (3) ossification in this young, proliferating tissue.

Barth (1895) placed a piece of incinerated bone in the peritoneal cavity of a cat. Six weeks later he found it penetrated by connective tissue and in several places by true bone lined by osteoblasts.

Pollack (1901), in examining lungs obtained at one hundred postmortem examinations, was able to demonstrate the presence of osseous nodules in sixteen cases. He expressed the belief that old scar tissue forms osteoid tissue and bone by metaplasia.

Sacerdotti and Frattin (1902) found bone plaques in the kidneys of three of four rabbits of which the renal vessels were ligated. In two cases the ureters were tied. True cortex, periosteum and endosteum were present.

Poscharissky (1905) produced bone in a rabbit's kidney in from three to four months by ligating the vessels.

Maximow (1906) found bone as early as five weeks after ligation of the renal pedicle.

Liek (1906) ligated the renal vessels of sixteen rabbits. In four he ligated the ureter as well as the vascular pedicle. He concluded that the necessary requirement for formation of bone is young connective tissue near deposits of calcium.

Bunting (1906), after studying sclerotic aortas, wrote: "The factors in metaplastic bone formation in vessels are extensive sclerosis with the presence of calcium deposits, traumatic or inflammatory disturbance in the calcified area, with penetration by granulation tissue and the formation of bone."

Harvey (1907) applied irritants to the wall of the aortas of rabbits to induce degeneration. Bone, haversian canals and marrow were formed, and Harvey stated: "New bone formation commences in areas previously necrotic. This process of new bone formation is one of metaplasia of connective tissue."

Buerger and Oppenheimer (1908) expressed their views as follows: "It is generally conceded that the presence of lime and young connective tissue is essential to heteroplastic bone formation. Due to some stimulus, vessels penetrate the diseased mediae, young connective tissue proliferates and comes in contact with lime deposits. True bone is formed."

Pearce (1909) wrote: "True bone was found in the scar tissue of the kidney in six animals. Bone formation occurred as thin lamellae in the scar tissue immediately beneath the mucosa of the pelvis."

Baschkirzew and Petrow (1912), on the basis of experiments on animals and of clinical observation, elaborated the theory that regeneration of bone takes place by metaplasia from the surrounding connective tissue cells. The majority of bone transplants soon die; then young connective tissue cells penetrate into the vascular and haversian canals and are converted into osteoblasts and bone cells. Preservation of the periosteum is not essential to the life of the transplant, but it evidently is useful in causing more rapid union between the transplant and the surrounding tissues, in hindering resorption of the transplant and in giving the first impulse to formation of new bone.

Todd (1912) wrote: "Osteoblasts do not enter skeletal tissue along the blood vessel tracks, but are fibroblasts or connective tissue cells which have undergone certain characteristic modifications and may or may not have passed through a chondroblast stage."

Strauss (1914) made ureters experimentally from the abdominal wall. Bone formed in the layer of the fascia transversalis. No degenerative changes had taken place where bone was formed. The bone that had formed closely resembled normal bone.

McWilliams (1914) stated: "Connective tissue seems to be essential in the formation of bone. Osteoblasts are indistinguishable from fibroblasts. The first occurrence in bone formation is the arranging of fibroblasts (osteoblasts) around a blood vessel. In this new fibrous tissue calcium is deposited by some unknown influence, which goes on to the formation of bone. . . . There is some other factor making for the life of grafts than the periosteum or contact with living bone; and this I take to be a sufficient blood supply."

Moschcowitz (1916) reported several cases of calcification or ossification in the ovary. "Blood vessels, osteoblasts, bone cells, and marrow (in large part at least) are merely differentiations of the mesenchymal cell unit," he wrote.

Neuhof (1917) wrote: "In fascial transplants into experimental defects in the urinary bladder, macroscopic plaques of true bone appeared. . . . That previous bone or periosteum is not necessary for the formation of new osseous tissue was, of course, demonstrated by finding such tissue developed in situations far removed from the skeletal system. . . . The periosteum-like layer ensheathing the bone plaques can be accounted for satisfactorily on the theory of metaplasia of adjoining connective tissue and similarly, metaplastic changes in connective tissue included between the bone trabeculae will explain the development of bone marrow."

Asami and Dock (1920) ligated renal vessels and ureters of rabbits, and bone plaques formed later. Young fibroblasts accumulated to form a membrane-lined structure. Formation of bone began in the loose vascular connective tissue, close under the transitional epithelium of the calices.

Phemister (1923) found that in fascial transplants to the bladders of dogs (the urine of which is always acid) bone always formed. In similar transplants in rabbits and sheep (the urine of which is alkaline) there was no calcification or ossification. Lime salts were deposited from the lymph or blood in the portion of the transplant bordering on the lumen, where nutritional conditions were poorest, necrosis was greatest and the acidity was increased by contact with the acid urine of the bladder.

Leriche and Policard (1926) stated: "1. The formation of bone is the result of a metaplastic change in the connective fundamental substance. This metaplasia takes place in three stages: (a) transformation of the connective tissue by an edematous infiltration with a multiplication of connective fibrils; (b) infiltration by a special substance, chemically undefined—the preosseous substance; (c) deposits in that substance of a calcareous mixture of calcium phosphates and carbonates.

"2. Osseous metaplasia can occur in all types of connective tissue; embryonal type, fibrous type, etc. The numerous forms of osseous tissue, as found among man and animals, are the result of that process.

"3. In osseous metaplasia, the cells do not play the part classically attributed to them, that is to say the osteoblasts do not secrete directly osseous substance between the cells. Such a conception is erroneous. The osseous transformation of connective tissue is a phenomenon independent of all cellular action. It is an interstitial and humoral process. . . . The periosteum is modified (to an embryonal state) by a change of circulation or by edema; it becomes then a ground for ossification. It is passively ossified—it does not make bone in an active manner."

Osseous metaplasia of connective tissue is a reversible process. Bone appears and disappears with the greatest facility. There is a continual state of unfixed equilibrium.

In transplantation of bone the formation of new bone depends on the resorption of the transplant. It seems that as a result of rarefaction of bone there is produced a localized oversupply of calcium, which provokes an osseous metaplasia in the surrounding connective tissue.

"The resorption of bone is specially directed by humoral phenomena, dependent on the circulatory activity in the bone."

Keith (1927) stated that many cases have been reported in which bone formed in the scars left by laparotomy. Osteoblasts, which are directly concerned in the formation of bone, are probably not transported by the blood stream. Fibrous tissue anywhere can produce bone if it reverts to embryologic fibroblasts (embryonal state) or edematous fibrils and if calcium is present. As the arteries proliferate, lamellae of bone appear around them. The cells which assume a bone-forming rôle are derived from the endothelium of the capillary system or from the reticulo-endothelium. Perhaps the action of an enzyme is necessary to stimulate this proliferation.

Huggins (1931) found that when the urine has been diverted from the bladder of the dog, bone still forms in a fascial transplant to the wall of the bladder. The bone forms only in the transplant, and the newly formed epithelium of the transplant is the essential factor in the osteogenesis.

Abbott and Goodwin (1932) stated that the mucous membrane of a dog's bladder when transplanted into muscle forms an epithelium-lined cyst wherein new bone is deposited after twenty days.

PURPOSE AND METHOD OF EXPERIMENTS

The presentation of such a time-worn subject as experimental transplantation of bone can be justified only if some different type of experimentation has been employed. Our efforts have been particularly along two lines. Our first purpose was to determine what difference, if any, could be noted in the rate and the type of healing of grafts taken from bone of different regions or different structures: (1) cortical bone of the tibia, (2) cancellous bone of the tibia, (3) spongy bone of the ilium, (4) periosteum and (5) chips of bone elevated in situ along the spinal column, as in the Hibbs fusion operation. Our second purpose was to determine what, if any, effect on the rate and the type of healing could be produced by "decalcification" of experimental animals.

Adult dogs were selected for all the experiments. The animals were in excellent condition. The dog's spinal column is not unlike that of man and is easily used for bone-grafting procedures.

The operations were performed under ether anesthesia with aseptic surgical technic. Spinous processes (usually four at a time) were exposed, and the dissection was carried down along the laminae, exposing them as far as possible, even to the articular facets. Bone grafts were then taken from the tibias, the entire thickness of the cortex being used. These grafts were divided into periosteal, cortical and endosteal or cancellous portions, and each of these portions was used as a transplant to the prepared bed along the spine, each being placed in a separate

portion of the prepared bed. In addition, a portion of the posterior crest of the ilium, including the posterior superior spine, was removed and used as a transplant. Thus, four separate pieces, three of bone and one of periosteum, were used in each operation, and each was placed in a separate part of the prepared bed along the spinal column.

Up to this point two animals had been used, and the same operation performed on each. After approximately thirty days the same procedure was repeated on each animal in another part of the spine. Thus in each animal we had two operative areas, so that there were four operative experiments. In addition, we carried out the Hibbs operation on two pairs of animals. This operation also was done twice on each animal at an interval of approximately thirty days. All of these experiments were repeated a like number of times on our four decalcified animals. Thus we were able to compare the amount of formation of new bone about the various types of transplants. The animals were killed approximately three months after the first operation; therefore, we had comparative data on transplants made two and three months previously.

All the animals were treated with sodium alizarine sulphonate (alizarine red) after the first operation in order to obtain vital staining of the specimens. This substance was used after the manner described by Bauer, Aub and Albright.

After each dog had been killed, the entire spinal column was removed. Sections were taken for microscopic study from each of the regions where a graft was placed. The remainder of the spinal column in most instances was macerated (in a solution of potassium carbonate 30 Gm. and sodium sulphide 15 Gm. for each liter of water) in order to get rid of the soft tissue and to allow the changes in the bone itself to be observed.

Roentgenograms were taken in most instances sixty and ninety days after the first operation. Studies of these roentgenograms in comparison with the specimens will be presented.

Microscopic sections of the regions of operation, showing the behavior of the different types of grafts, have been made. The picture differed both as to the length of time in situ and as to the type of graft. The calcium balance of the dogs also differed. Comparative study of these sections offered some interesting facts.

In order to study the effect of a decreased calcium content in the dog, certain animals were given diets low in calcium, composed of boiled rice, fish, distilled water and ammonium chloride. This regimen was continued for approximately thirty days before the first operation was performed. The diet was maintained up to the time of the first operation, after which a normal diet was resumed. By this means, some degree of decreased or negative calcium balance could be obtained. It is our belief that this decrease could be carried much further, with perhaps a more striking effect on the behavior of the transplants.

STUDY OF SPECIMENS

The study of the gross specimens revealed in all instances except two solid union between the bone graft and the bone of the host. The periosteal grafts, however, gave no evidence of formation of new bone. In the two instances in which grafts were not united and there was little or no evidence of formation of new bone, there were infected wounds. In all instances except these two, the wounds had healed solidly and there was no evidence of infection. It should be noted that no type of fixa-

tion was used in any of these cases. This simplified very much the handling of the experimental animals, and it is hard to see that the results to be described were in any way affected.

The effect of the sodium alizarine sulphonate was easily noted in all cases. Not only the newly formed bone but the surrounding bony structure, wherever it had been touched by the operative procedure, was stained bright red. Thus the spine and the tibias as well seemed to be stained as far back as the soft tissues had been reflected at the time of the operation. No difference could be noted in the different types of transplants, nor could any appreciable difference be made out between transplants in normal and those in decalcified animals, so far as the amount of vital staining was concerned. The staining of the new bone deposited was vivid in most instances.

In the study of the microscopic sections, much more accurate information regarding the relative stages of formation of new bone was gained. A description of these changes follows.

Cortical Grafts.—There was a definite tendency toward diminished condensation of the transplanted bone. However, in none of our cases was there what might be called complete death of the graft, or anything approaching it. The grafts gave evidence of union in most instances, but at the end of three months union was not so extensive as in the grafts taken from cancellous bone. The type of new bone formed in the decalcified animals seemed much more "active"; that is, this bone was in most instances made up of chondro-osteoid tissue which was rapidly turning into bone (figs. 1 and 2), whereas the tissue binding the cortical grafts to the spinous processes in the animals that were not decalcified was firm connective tissue, not giving evidence of much actual formation of new bone (fig. 3). In spite of this, in all instances but one gross examination of the specimens disclosed firm union between the graft and the host, apparently with laying down of new bone, or at least with deposition of calcium in the tissues connecting the graft to the host, as demonstrated by the presence of the alizarine red in the tissue.

Grafts from Cancellous Bone of the Tibia.—These transplants were taken from the tibial grafts; that is, the endosteal or cancellous portion of each tibial graft was removed and implanted along the laminae as a separate graft. On gross examination all of these grafts except one were well united, and all were well stained. In the microscopic sections the appearance was so similar to that shown by the grafts taken from the cancellous bone of the iliac crest that one description will suffice.

Grafts from the Crest of the Ilium.—These grafts were cut with an osteotome from a point 1 cm. below the posterior superior spine, and

ran forward along the crest of the ilium for from 3 to 4 cm. Such a graft is almost pure cancellous bone, although it is a much heavier type of cancellous bone, with its trabeculae more closely spaced, than that seen in the endosteum of the tibia. That is, the individual trabeculae

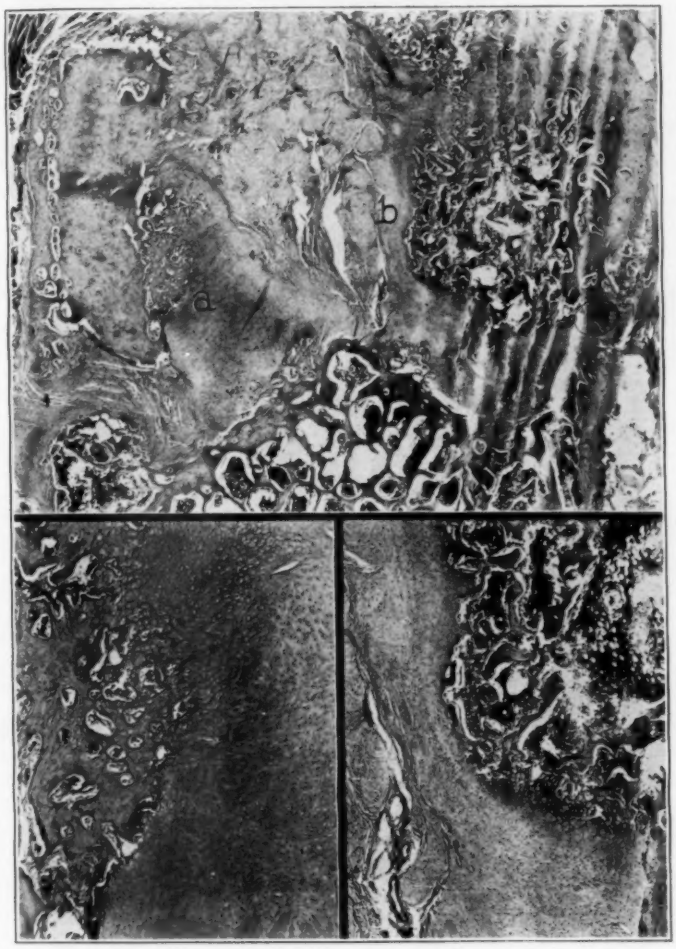

Fig. 1.—Section from a decalcified animal sixty-one days after operation. In the cortical graft (*a*) the vascular spaces are of increased size because of decalcification. The view of area *b* under higher power magnification shown at the left below gives marked evidence of formation of chondro-osteoid tissue. The cancellous graft (*b*) shows similar changes, with active formation of chondro-osteoid tissue. A view of the area *b* under higher power magnification is seen at the right below.

of the iliac crest, although no larger than those of the tibia, are more numerous and more closely packed together, giving the appearance that the bone is much heavier. The union between these grafts and the

spinous processes and laminae was without exception the best that occurred with any type of graft (figs. 3 and 4). In many instances, new bony trabeculae had formed in sixty days or less, and the grafts seemed solidly united to the bone of the host. The trabeculae were

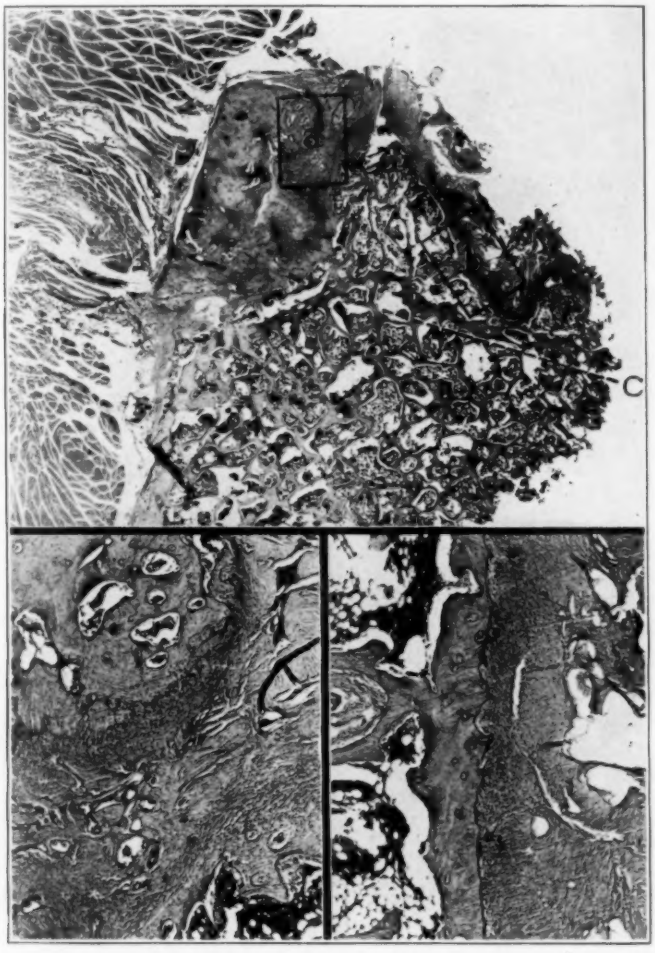

Fig. 2.—Section from a decalcified animal eighty-two days after operation. The cortical graft (*a*) is shown at a later stage than that represented in figure 1. There is less evidence of osteoporosis. The tissue connecting the graft to the host is more advanced bone. A view of area *a* under higher power magnification is seen at the left below. The bed of the periosteal graft (*b*) shows no formation of new bone. A view of area *b* under higher power magnification is seen at the right below. The spinous process of the host is designated by *c*.

numerous and firmly bound to the spinous processes and laminae. On gross examination this was easily demonstrable, and the microscopic appearance seemed to bear it out.

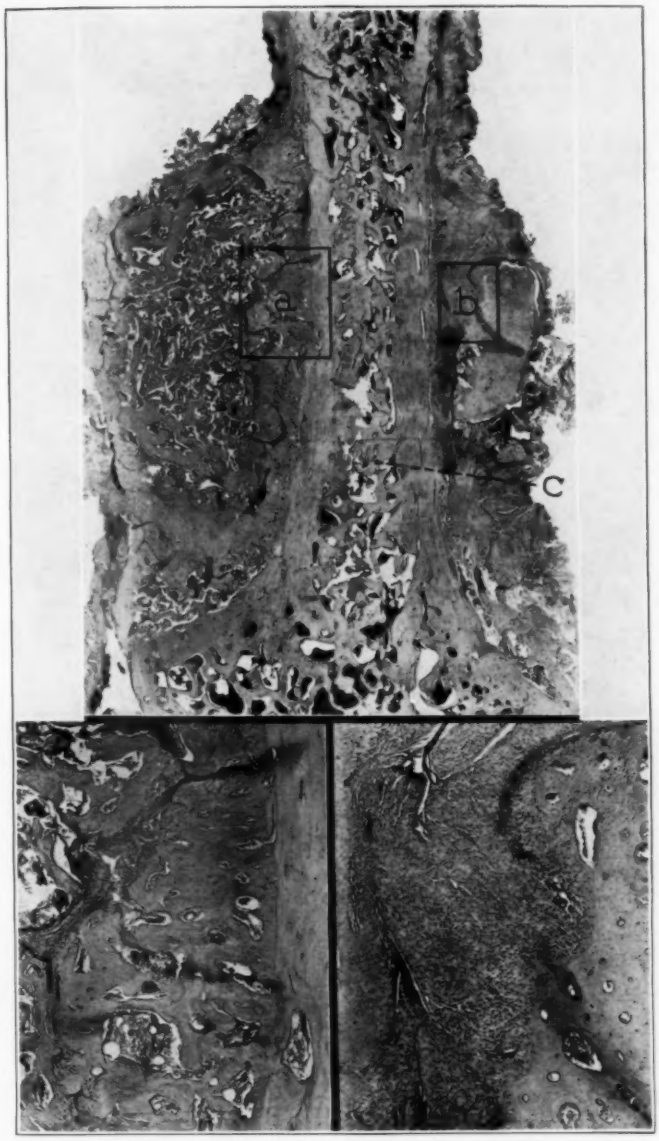

Fig. 3.—Section from a normal animal eighty-eight days after operation. There is firm bony union between the cancellous graft (*a*) and the bone of the host. A view of area *a* under higher power magnification is seen at the left below. The cortical graft (*b*) shows only fibrous union with the bone of the host. A view of area *b* under higher power magnification is seen at the right below. The spinous process of the host is designated by *c*.

Grafts of Periosteum.—In none of our experiments did the transplantation of periosteum seem to result in formation of new bone, either from the transplant or from the host tissues (figs. 2 and 4). Before too much importance is placed on this finding, however, it must be remem-

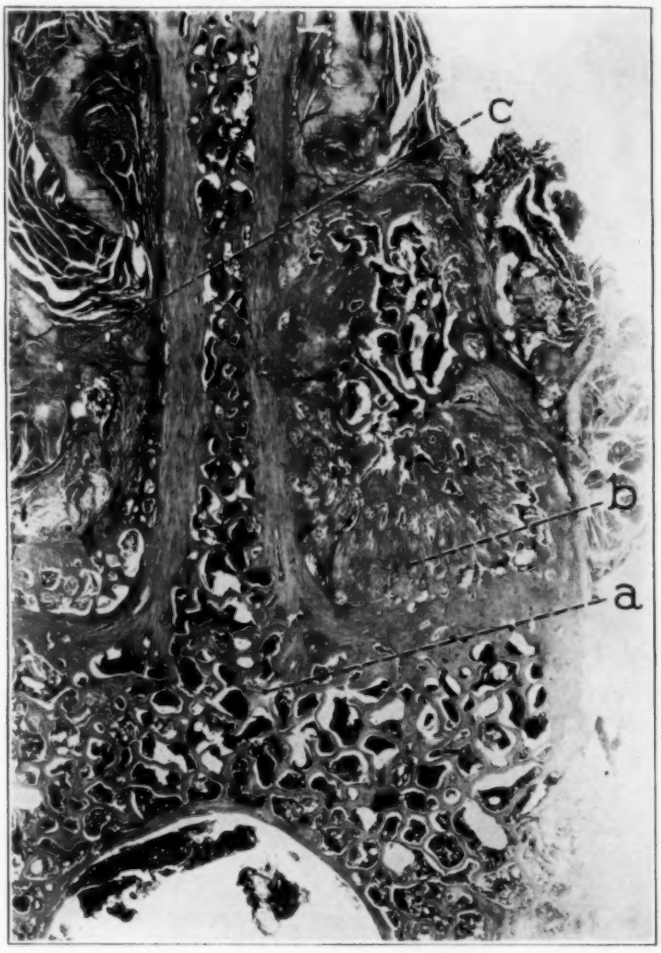

Fig. 4.—Section from a normal animal fifty-six days after operation. The spinous process of the host is designated by *a*. The cancellous graft (*b*) is united to the bone of the host by trabeculae of completely formed bone. The region (*c*) where the periosteal graft was implanted gives no evidence of formation of new bone.

bered that none of our animals was young. The periosteal transplant in all cases was obtained from the front of the tibia from which the graft was removed. In most instances it consisted of a thin piece of fibrous

tissue, without much blood supply, which separated easily from the tibia. It differed much more markedly from the periosteum of young animals than the periosteum of the tibia of an adult person differs from that of a young or adolescent person. It is our feeling, and this is cor-

Fig. 5.—Section from a decalcified animal sixty-two days after a Hibbs operation. The spinous process of the host is designated by *a*, and a chip of bone with no formation of new bone by *b*. There is some foreign body reaction (*c*) between the chip of bone and the host.

roborated by many writers, that the periosteum of a young person under certain conditions may stimulate formation of new bone but that the periosteum of older persons, at least on the shafts of the long bones where no muscular attachments are found, is a thin, almost nonfunctioning, ligamentous substance.

Bone Chips.—Experiments with bone chips were performed to determine what, if any, comparison could be drawn between the osteogenesis produced by operations like the Hibbs spinal fusion operation and that following operations in which bone grafts are employed. It has been demonstrated that the Hibbs operation will produce satisfactory bony fusion. However, in these experiments we were unable to demonstrate as extensive formation of new bone as occurred in the experiments with bone transplantation. Many of the chips when examined microscopically gave evidence of new bone forming around them. On the other hand, many of them failed to exhibit any evidence of formation of new bone, and in some instances there appeared to be death of some of the bone in the shaving and a foreign body reaction around it (fig. 5). In all instances, on gross examination there was fairly good staining by alizarine red but very little solid ankylosis.

PARTICULAR CONSIDERATION OF SPECIMENS FROM DECALCIFIED ANIMALS

Active reduction of the proportion of calcium in the skeleton is possible and, by the means which we used, fairly simply accomplished. Measurement of the amount of decalcification thus produced is much more difficult, and such a procedure seemed unnecessary in these experiments.

In most instances, the reduction was sufficient to allow one to detect a distinct difference from the way in which the normal bone cut at operation. We have already noted that the amount of red stain deposited in the tissues by the alizarine red in circulation was the same whether the animal was decalcified or not. On the other hand, in all cases in which satisfactory microscopic sections could be obtained, a particularly active osteogenic process seemed to be going on in the bone of the decalcified animals. This was shown either by the extensive formation of new trabeculae or by the active formation of osteoid tissue.

The chemical changes which take place must definitely affect the formation of new bone. Whether or not in the process of decalcification the tissues of the host, as well as those of the transplant, are so altered as to hasten the deposition of calcium when the way is prepared by adding more calcium to the diet we cannot state positively. The mechanism is perhaps purely circulatory, although the exact relationship of the circulation to decalcification and recalcification is as yet not understood.

It was noted in most of these specimens that decided widening of the haversian spaces had taken place in the grafts as well as in the tibias of the decalcified animals. This would be expected under the circumstances and was merely a manifestation of the changed content

of calcium. That these two processes were both influencing the formation of new bone seems more than likely. That they represent more than one chemical or physiologicochemical process is also more than likely. The atrophy of bone incidental to the entire process makes the grafts somewhat more permeable to the invasion by new blood vessels that is necessary for osseous growth. The decreased content of calcium adds somewhat to this effect, and at the same time it seems to us that it probably leaves the new bone-forming tissue, which is the basic substance of the bony framework, in a more receptive state when the increased amount of calcium is poured into the tissues from the blood stream. Aub and his co-workers have shown that the trabeculations furnish a readily available supply of calcium, that their number and size may be appreciably diminished by a process similar to that which we have used, and, conversely, that they may be readily built up by the addition of calcium to the diet. It seems reasonable to believe, therefore, that in a medium somewhat depleted of calcium salts the framework of the bone may be laid down more easily, and that when the necessary calcium salt is supplied it is more readily taken up and deposited in this framework, making new bone.

STUDY OF THE CUT EDGES OF THE BONE

We had used a motor saw, and the behavior of the cut edges of the bones from which the grafts were taken interested us. It has been suggested from time to time that the use of a motor saw impairs the osteogenic properties of the bone, either by overheating the bone and thus killing the osteoblasts or by packing the margins of the cut with bone sawdust and thus decreasing the permeability of the bone. In examining these tibias grossly at autopsy we found most of the defects (except in the two cases in which infection had taken place) to be filled with bone. Three months after the original operation the filling was complete; two months after operation, filling was not complete, but there was a remarkable amount of regeneration. Studies of sections taken through these defects disclosed solid bony union between the margin of the defect and the newly formed bone along one border. At the other border this was broken through, probably by manipulation. In some of the sections union was much less marked than in others. Although we cannot prove from these facts that there is no deleterious influence of the motor saw on the bone-forming properties of the graft, we can at least say that these properties are not consistently destroyed. Thus regeneration of bone will not be interfered with along the cut edge.

ROENTGENOGRAPHIC CHANGES

Study of roentgenograms disclosed two important facts. In the first place, there was decreased density of the grafts at a certain stage. This probably represents a stage when vascularization of the graft from the

host had been accomplished and through this increased vascular supply the density of the bone was diminished. As the vascular bed was laid down and completed, new bone replaced the old bone of the graft, and a new graft was formed, or at least what appeared to be a new graft. Such a process has been noted many times, not only clinically but in experiments on animals. In the second place (and this seems to us of considerable importance), the decreased density of the graft was appar-

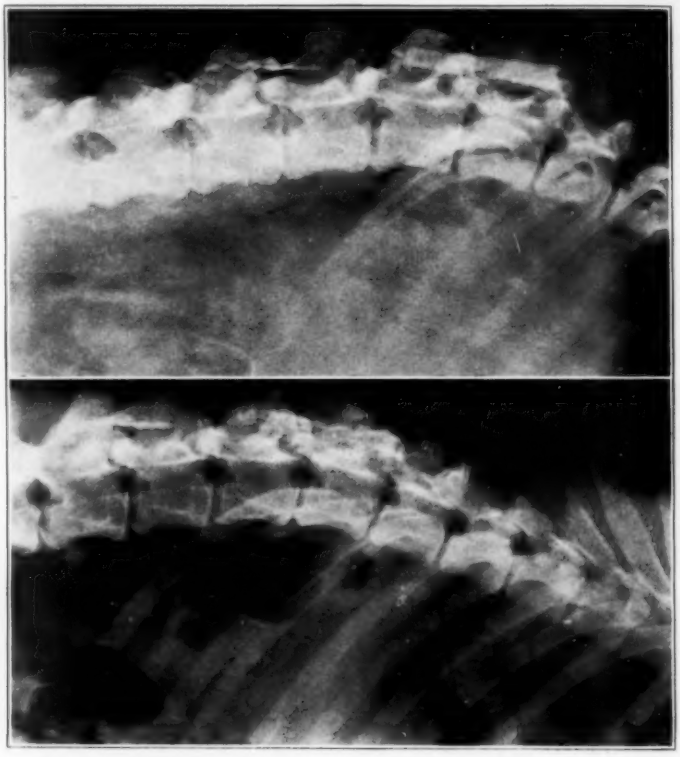

Fig. 6.—Roentgenograms of a normal animal. The film shown above was taken two months after operation. A cortical graft is seen on the right; the bone is still dense. On the left, the faint outline of a cancellous graft can be seen. The film shown below depicts the same region thirty days later. The cortical graft has undergone marked atrophy, whereas the cancellous graft shows much more plainly. It has reestablished its bony consistency.

ent much earlier in the iliac grafts than in the cortical tibial grafts (fig. 6). This indicates that the cancellous bone of the ilium was more easily infiltrated by the vascular network which invades the graft than the tibial cortical bone. Furthermore, at the stage when the cortical grafts were of diminished density (that is, at three months) the iliac grafts had reestablished their bony content, the final consistency thus being much more quickly acquired than when cortical grafts were used.

Little difference was noted between the roentgenograms of the decalcified animals and those of the normal animals. This would be expected, for it is well known that loss of lime salts from bone must be considerable to cause appreciable diminution in penetrability to roentgen rays. Roentgenograms of the tibias disclosed that repair of the defect was apparently complete at the end of three months in most instances.

COMMENT

The classification of the theories of bone growth as outlined in this paper merely affords a working basis for comparison and cannot be regarded as rigid. As a convenience, however, it seemed to offer distinct help to us. Our own theories coincide with the more modern ones of this group; that is, that the union of grafts and probably any new formation of bone are largely due to transformation of local cells into a matrix, or basic substance, which under certain stimuli adds to itself the calcium and other salts necessary for its transformation into bone. Such a conception is simple, and we cannot elaborate it on a chemical basis. From the practical standpoint, it is to be noted that this process is apparently more easily accomplished when the transplant is of cancellous bone, probably because the cancellous bone offers a medium much more readily permeable by this matrix from the host and its calcium may be more easily mobilized and redeposited.

Besides this, we are convinced that the process of reducing the calcium content of the bone may hasten its union in a transplanted position. This may be due, again, to the fact that a decalcified graft is more readily permeable by this matrix, but we feel that an added stimulus is brought about by the chemical change of decalcification.

SUMMARY AND CONCLUSIONS

1. Periosteal transplants in old animals do not produce new bone.

2. Cortical transplants do not completely die but unite slowly with the bone of their host, and decreased calcification is seen roentgenographically at the end of three months.

3. Cancellous bone unites more quickly and more firmly than cortical bone, whether taken from the cancellous bone of the ilium or from the endosteum of the tibia. It gives evidence of increased calcification roentgenographically at the end of three months.

4. Animals placed on a "decalcifying" diet until the time of the transplantation gave evidence of decidedly more active production of new bone both around the cortical and around the cancellous transplants.

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CHOLECYSTITIS DUE TO BACILLUS AEROGENES-CAPSULATUS

REPORT OF A CASE WITH NINE CASES FROM THE LITERATURE

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Bacillus aerogenes-capsulatus has a wide distribution in nature. It is found in soil and sewage water and in oysters and other shell fish, milk, cheese and various other foodstuffs. It is present in the feces of all domestic animals and a large number of wild animals. It has been cultured from the skin of normal persons, the mouths of new-born infants, the normal salivary glands and pancreas, the normal urine and the vagina, and from the circulating blood in puerperal sepsis, chorea and typhoid fever, as well as in other diseases in which injury of the intestinal mucosa occurs. It is present in the human intestine normally, and is usually limited to the cecum and colon but is occasionally found in the small intestines. It is less common in nursing babies and more abundant in old age. It has, however, been found in the new-born and is normally present in normal nursing infants, but it is more common in childhood and is a common inhabitant, perhaps the most abundant anaerobe, in the intestines of adults. These and other localizations of B. aerogenes-capsulatus were cited by Simonds,[1] who called attention to the high degree of natural immunity which man enjoys against this organism. He quoted Welch, who stated that there is good reason to believe that intact tissues of man in health possess marked resistance to the gas bacillus. Simonds' bibliography comprises 476 references.

B. aerogenes-capsulatus has been found in normal bile at autopsy.[2] This association was noted by Branch,[2a] who pointed out that this micro-organism, which is indigenous to areas drained by the portal system, is apparently held in abeyance by healthy living tissues. In poorly preserved bodies and during the summer months, the bacillus

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1. Simonds, J. P.: Studies in Bacillus Welchii, Monograph, Rockefeller Institute for Medical Research, 1915, vol. 5.

2. (*a*) Branch, C. F.: A Group of Diseased Gall Bladders, New England J. Med. **201**:308 (Aug. 15) 1929. (*b*) Gilbert and Lippmann: Zentralbl. f. Chir. **30**:609, 1903.

invades and damages tissues at death, before fixation is accomplished. The presence or absence of bacteria, particularly B. aerogenes-capsulatus, in the walls and contents of normal and diseased gallbladders has been variously reported. Thus in a series of 100 cultures from gallbladders removed at operation, one series of 32 positive cultures showed no Bacillus welchii.[3] In another series [4] of 270 similar cultures, there were 58 which were positive for bacteria but showed no B. welchii. On the other hand, in 210 cases in which the gallbladder was removed at operation, Branch [2a] found B. aerogenes-capsulatus in the wall of the gallbladder in 8 cases; in the bile, in 5 cases, and in the stones, in 7 cases. It was never the predominating organism. Stolz [5] reported 3 cases of gallstones and inflammation of the biliary ducts and liver in which the gas bacillus was identified with Bacillus coli and other bacteria.

Active cholecystitis in which B. welchii has been recovered in pure culture showing a characteristic pathologic condition at postmortem examination or at operation is not often reported. In the following collection we have not included cases mentioned casually, with no criteria for diagnosis,[6] or cases in which a culture of the blood or stones yielded B. aerogenes-capsulatus even in pure culture [7] unless pure culture of the gallbladder showed the same micro-organism. We have excluded cases in which no clinical data are given, such as the cases cited in reports of the examination of gallbladders removed at operation.[8] That one must be careful in ascribing a pathologic condition to so widely distributed a micro-organism has been pointed out by Wahlberg.[9]

Recently the authors have been able personally to observe a case in which the clinical course and the postmortem observations were such

3. Johnson, W. O.: One Hundred Consecutive Cholecystectomies, Am. J. M. Sc. **170**:181 (Aug.) 1925.

4. Blalock, A.: Biliary Tract Disease, Bull. Johns Hopkins Hosp. **35**:391 (Dec.) 1924.

5. Stolz, A.: Ueber Gasbildung in den Gallenwegen, Virchows Arch. f. path. Anat. **165**:90 (July 16) 1901.

6. Andrew, E., and Hrdina, L.: Arch. Surg. **23**:201 (Aug.) 1931. Libman, E.: On Some Experiments with Blood Cultures in the Study of Bacterial Infections, Bull. Johns Hopkins Hosp. **17**:215 (July) 1906.

7. Baugher, A. H.: The Bacillus Aerogenes Capsulatus in Blood Culture with Recoveries, J. A. M. A. **62**:1153 (April 11) 1914. Greeley, H.: Idiopathic Bacillus Aerogenes Capsulatus Infection, Bull. Johns Hopkins Hosp. **29**:231 (Oct.) 1918.

8. Gordon-Taylor, G., and Whitby, L. E. H.: Bacteriological Study of 50 Cases of Cholecystectomy with Special Reference to Anaerobic Infections, Brit. J. Surg. **18**:78 (July) 1930. Branch.[2a]

9. Wahlberg, K.: Die Gasbazilleninfektion der Gallenblase, München. med. Wchnschr. **74**:2095 (Dec. 9) 1927.

as to give a characteristic picture and leave no doubt that B. aerogenes-capsulatus was the cause of a rapidly fatal cholecystitis. It is the purpose of this paper to report the case and review 9 other cases which were found in the literature.

REPORT OF CASES

Case 1.—The first report of cholecystitis due to B. aerogenes-capsulatus was that of Cottam,[10] in 1917. The patient was a woman, aged 41, who on March 6, 1917, had a severe pain in the lower thoracic region and in the upper part of the abdomen, particularly in the midline, accompanied by vomiting. The abdomen was tender; there was no rigidity. The temperature was 98.4 F. On the following day the pain was localized at the umbilicus and McBurney's point. There was rigidity in the right lower quadrant as well as in the right upper quadrant, with general tympanites. Two days after the onset, the symptoms shifted entirely to the upper region of the abdomen. Operation was performed on this day. The gallbladder was distended and deep red. Near the fundus was a greenish, blistery, gangrenous, oval area which measured 1.5 cm. in the short, and 2.2 cm. in the long, diameter. A short distance behind this was a similar area. There were five small gallstones. The morphologic and cultural findings indicated conclusively that the organism was B. aerogenes-capsulatus.

Case 2.—In 1922, not knowing of Cottam's case, Halle and Marquézy[11] reported what they believed to be the only case of gangrenous cholecystitis due to B. aerogenes-capsulatus. The patient, a woman, aged 60, suffered a sudden, violent pain in the right upper quadrant radiating to the right shoulder, which caused her to vomit. The pain subsided but left her weak and indisposed. Five days later, after she had taken a cathartic, the symptoms recurred. Fever and meteorism developed. On the third day of her second attack, she had jaundice, violent pain in the region of the gallbladder and respiratory signs and symptoms which confused the picture. On the fourth day, operation was performed under local anesthesia. There was no pus in the abdominal cavity, but the omentum showed fat necrosis like that in certain forms of gangrenous pancreatitis. One of the areas removed for biopsy showed a large, gram-positive anaerobe. When the biopsy specimen was macerated and injected into a guinea-pig, the animal died within ten hours, and B. aerogenes-capsulatus was recovered from the liver and the spleen. The patient died two days later. The gallbladder contained fluid and gas but no stones. It was ulcerated and showed gangrenous lesions. No secondary infection was apparent.

Case 3.—During the same year, Lereboullet[12] reported briefly a case of perforating cholecystitis with fetid pus. The patient had an old biliary calculus. Death followed a "peritoneal episode comparable to that described by Halle and Marquézy." There were gangrenous perforation and peritonitis with fetid pus. The micro-organism obtained in pure culture was studied by Zuber, who found it to be B. aerogenes-capsulatus.

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10. Cottam, G. G.: Gangrenous Cholecystitis with Report of a Case Due to the Gas Bacillus, Surg., Gynec. & Obst. **25**:192 (Aug.) 1917.

11. Halle and Marquézy: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:49 (Jan. 13) 1922.

12. Lereboullet: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:257, 1922.

CASE 4.—In 1925, Kirchmayr [13] published what he thought to be the first case of infection of the gallbladder due to the gas bacillus. The patient, a man, aged 64, suffered an attack of cramplike abdominal pain which subsided after a few hours. Fourteen days later he was seized with sudden abdominal pain. The abdomen was distended. There were circumbscribed tenderness in the right lower quadrant and marked tenderness in the region of the gallbladder. Perforation was feared. An operation was accordingly performed on the third day, following the second attack of pain. When the abdomen was opened, gas with a putrid odor escaped. The gallbladder was as large as a fist and adherent. The fundus showed irregular, delimited necroses from the size of a pinhead to more than that of a lentil. When the gallbladder was aspirated, gas and bloody bile were obtained. Attempted ligation of the neck of the gallbladder and of the cystic artery separately tore the friable tissue in both cases in such a manner that gauze packing was resorted to. The enlarged gallbladder was edematous in all layers and was so infiltrated by small gaseous vesicles that it crepitated. In many places the mucosa was necrotic. In addition to bloody, foul-smelling bile, the gallbladder contained sand with granules as large as a hempseed. The wall of the gallbladder contained multiple older abscesses of the wall, and the mucosa was discolored by parietal phlegmons. The wall showed acute phlegmonous destruction. The culture of the bile showed a gram-positive anaerobe of the Welch group in pure culture. The patient made a rapid recovery.

CASE 5.—In 1927, Gould and Whitby [14] reported the case of a woman, aged 46, who suffered severe, paroxysmal pain in the right upper quadrant for two days. The temperature, which at the onset was 99 F., rose to 101.2 F. Operation disclosed a tense, injected gallbladder with rancid contents. This was removed. There was slight uniform thickening of the walls, with injection of the coats. There was patchy gangrene of the mucosa so that the latter presented a mosaic of gangrenous areas surrounded by intensely congested but living mucosa. A smear showed large quantities of gram-positive, thick bacilli which were identified as B. welchii by injection into guinea-pigs. Six stones were found; these were crushed, and B. welchii were cultured from the inside. The patient recovered.

CASES 6 and 7.—During the same year, Wahlberg [9] published the report of a case. In this patient, a woman, 36 years old, two months following miscarriage and two days after curettage, there suddenly developed a severe pain below the right costal arch and slight jaundice with chill. A symptomatic recovery occurred, but five weeks later she presented the symptoms of sudden, acute cholecystitis with fever and vomiting. There was a tumor in the right upper region of the abdomen, extending to the umbilicus. At operation there was no evidence of infection with the gas bacillus, but the bile, the wall of the gallbladder and the excised fragments of liver showed pure cultures of the gas bacillus. It was impossible to demonstrate the bacillus in duodenal contents removed by intubation. Cultures of the blood and the urine were sterile. The patient recovered in three weeks.

Wahlberg also reported briefly a case in which the gallbladder had perforated. Pure cultures of the gas bacillus were made from a large abscess and from the bile. The patient recovered.

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13. Kirchmayr, L.: Ueber einen Fall von Gasbrand der Gallenblase, Zentralbl. f. Chir. **52**:1522 (July 11) 1925.

14. Gould, E. P., and Whitby, L. E. H.: A Case of B. Welchii Cholecystitis, Brit. J. Surg. **14**:646 (April) 1927.

Case 8.—In 1929, Spitznagel [15] reported the case of a man, aged 50, who was always well until four days before he was seen, when a sudden, severe pain developed in the region of the gallbladder which subsided after a few hours. Four days later jaundice developed and he applied for treatment. On the second day, under observation, severe colic similar to the first attack developed, and he rapidly became very ill. The jaundice was intense, and the temperature rose to 39.9 C. (103.3 F.). The patient was judged too ill for operation, and in a few hours he died. Necropsy was performed sixteen hours later. The subcutaneous tissues contained gas. The skin of the entire body was like a cushion. When the abdomen was opened, gas escaped with a loud noise. The abdominal cavity contained dirty, hemorrhagic fluid. The gallbladder was markedly enlarged. The serosa was opaque and covered with fibrinous deposits. It was loosely adherent to surrounding structures, and here and there were discolored, necrotic spots. The lumen contained discolored and dirty brown bile without bubbles of gas. The mucosa was largely necrotic, containing dirty brown, friable islands. The wall was thinned, the necrotic spots forming the thinnest part. No gallstone was found. The ducts were patent. The other organs, except the gastro-intestinal tract, showed gaseous edema. Bacterial examination of bile and blood gave pure cultures of the gas bacillus; whereas other organs showed simple necrosis and gaseous edema, sections from the gallbladder showed that the mucosa was lacking or demonstrable only in the shadowy outline. The mucosa was entirely necrotic and infiltrated with gram-positive rods which were also present in the deeper layers. The capillaries of the gallbladder were congested and partially thrombosed.

Case 9.—In 1931, Hegner [16] reported a case in a man, aged 62, who three weeks before he was first seen, had an attack of pain like colic due to a gallstone. Sixteen days later the pain recurred. Slight jaundice developed, and the patient suddenly became very ill and died. From around the wall of the gallbladder and around the tumor mass B. welchii was obtained in pure culture.

Case 10.—Our patient, a man, aged 63, a native of Poland, was admitted to the Third (New York University) Medical Division of Bellevue Hospital on Jan. 18, 1932. He gave a history of having been kicked in the chest by a horse nineteen years before. After that he did not consider himself well enough to work. Five years earlier the right kidney had been removed because of blood in the urine. Fifteen years before, the right leg had been operated on for "blood poisoning."

On admission, the patient's temperature was normal, and his complaints were mainly of pediculosis vestimentorum. On examination he appeared weak and prostrated without apparent cause. The blood pressure was 170 systolic and 110 diastolic. The liver was readily palpable below the costal margin. It was not tender.

On January 20, forty-eight hours after admission, the patient had a chill, and the temperature rose to 104 F. He became cyanotic and dyspneic. The leukocyte count, which was 7,200 on admission, rose to 17,000. Prostration, dyspnea and cyanosis continued, and the patient died on January 22.

Autopsy (Performed Four Hours Post Mortem).—The body was that of an elderly white man, well developed and well nourished. The abdomen appeared distended. The regional lymph nodes were not palpably enlarged. There was no icterus.

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15. Spitznagel, K.: Gasbazillencholezystitis, Wien. med. Wchnschr. **79**:461 (March 30) 1929.

16. Hegner, C. F.: Gaseous Pericholecystitis with Cholecystitis and Cholelithiasis, Arch. Surg. **22**:993 (June) 1931.

On section the subcutaneous fat was moderate in amount. The peritoneum was smooth and glistening. There was no free fluid. There was marked gaseous distention of the intestines.

Lungs: The lungs were voluminous; the pleural surfaces were adherent by dense bands of fibrous tissues. There was about 150 cc. of straw-colored, clear fluid in each sac. On section there were no notable changes except many areas of bullous emphysema.

Heart: The pericardium was natural. No changes were visible to the naked eye on examination of the myocardium, the endocardium and the valves, with the exception of slight atheromatous changes in the aortic leaflet of the mitral valve. A small bubble of gas about 5 mm. in diameter was seen beneath the intima on the ventricular aspect of the posterior aortic cusp. The bubble ruptured on pressure,

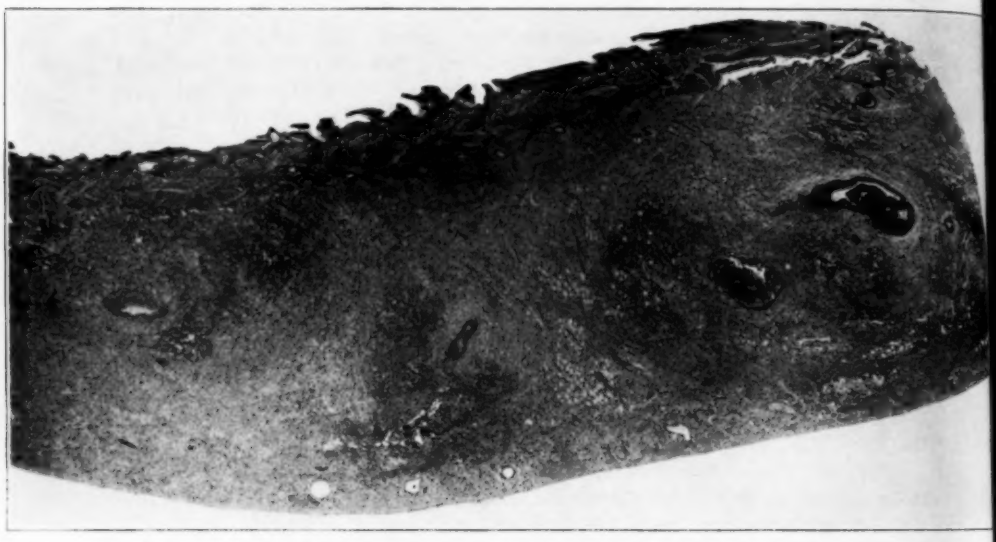

Fig. 1.—Low power photograph (Leitz Summar, 35 mm.) of a section through the wall of the gallbladder, showing the loss of lining epithelium, the thickening of all of the coats, thrombi in the vessels and abscesses.

revealing a break in the endothelial surface. The coronary arteries were sclerotic throughout.

Aorta: There was marked hemolytic staining of the intima, and a small subintimal hemorrhage was found in the arch of the aorta. There were numerous areas of atheroma with calcification throughout the aorta.

Gastro-Intestinal Tract: There were numerous small hemorrhages in the mucosa of the stomach. There were no ulcers. The small intestine and the large intestine showed marked dilatation. The mucosa and muscularis showed no changes.

Pancreas, Spleen and Liver: The pancreas was normal; the spleen, soft and slightly enlarged, but otherwise intact. The liver was enlarged and weighed 2,000 Gm. The capsule was smooth. On section, bile containing many gas bubbles exuded from the larger bile ducts, and numerous stones were found in all the visible biliary passages. The parenchyma of the liver was opaque, dull and grayish brown, and the markings were obscure. No areas of autolysis were visible. The

gallbladder was enlarged and markedly thickened. On palpation crepitus was made out within the gallbladder, and on section a foamy, greenish fluid escaped. The gallbladder contained many small faceted stones. When the surface was washed, numerous deep ulcerations were seen, many of which had hemorrhagic bases. The cystic and common ducts were dilated and patent. They contained stones and frothy bile.

The rest of the autopsy revealed no relevant changes.

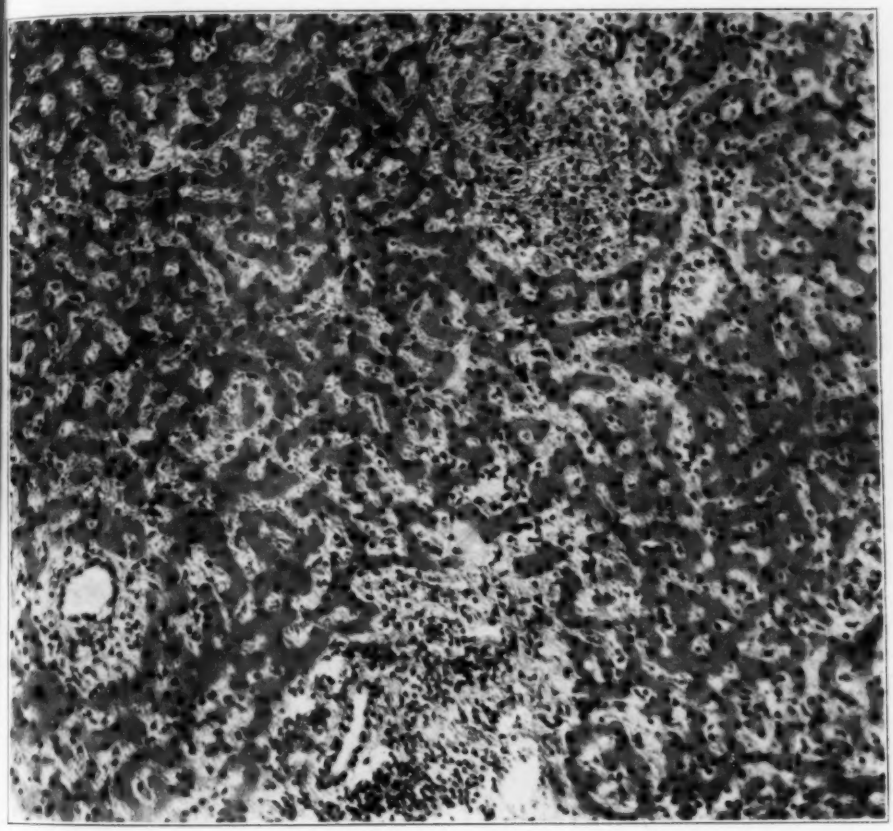

Fig. 2.—Low power photomicrograph of a section of the liver showing the low grade periportal hepatitis and, in the upper part of the field, a focus of parenchymatous degeneration.

Microscopic Report.—Gallbladder: There was marked edema of all the coats of the gallbladder. The lining epithelium was completely gone; only a few villi were recognized, and there were numerous ulcers which extended into the muscularis. There was infiltration of the coats by lymphocytes, histiocytes and polymorphonuclear leukocytes, and numerous small abscesses were seen in the wall with formation of calculus in the deeper crypts. Numerous arteries showed thrombosis, and there was edema of the vascular coats with infiltration by polymorphonuclear leukocytes.

Liver: The lobules were readily made out except in areas in which the parenchyma had been autolysed or compressed by gaseous formation. Numerous areas showed focal necrosis of the hepatic cells, some of which were central and others of which were portal in location. The cells were miliary in size and were not associated with cellular reaction. Most of the portal areas showed a slight increase in connective tissue and moderate infiltration by lymphocytes and histiocytes. There were no normal bile ducts. Almost every duct contained large gram-positive rods, detritus, desquamated epithelial cells and some bile pigment.

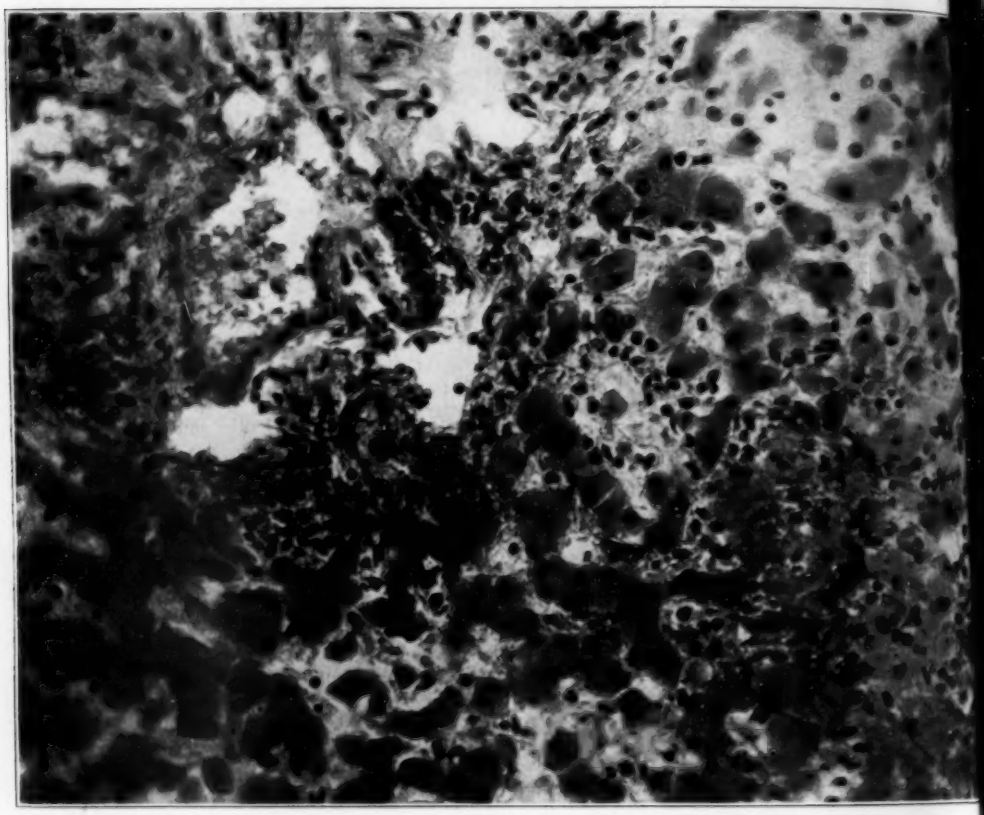

Fig. 3.—High power photomicrograph of the portal area showing the bacteria in the bile ducts and desquamation of the lining epithelium. Note the infiltration by mononuclear cells.

Occasionally a lymphatic channel was encountered, choked with bacteria, and an occasional area was found within the hepatic lobules which showed large clumps of bacteria in the sinusoids. The apparently intact hepatic cells showed various changes from slight fatty metamorphosis to karyorrhexis. The hepatic arterioles showed moderate sclerosis, but none of them was necrotic. There was an extensive deposit of pigment in all the sections examined, both in Kupffer's cells and in the cells of the central cords. Most of the pigment was golden brown and did not

give a positive reaction for iron. Evidence of hemolysis was seen in the finding of large amounts of scattered pigment free in the sinusoids and blood channels.

Sections of the other organs showed no notable changes.

Bacteriologic Examination.—Cultures made from the gallbladder and the heart's blood at necropsy revealed B. welchii in pure growth.

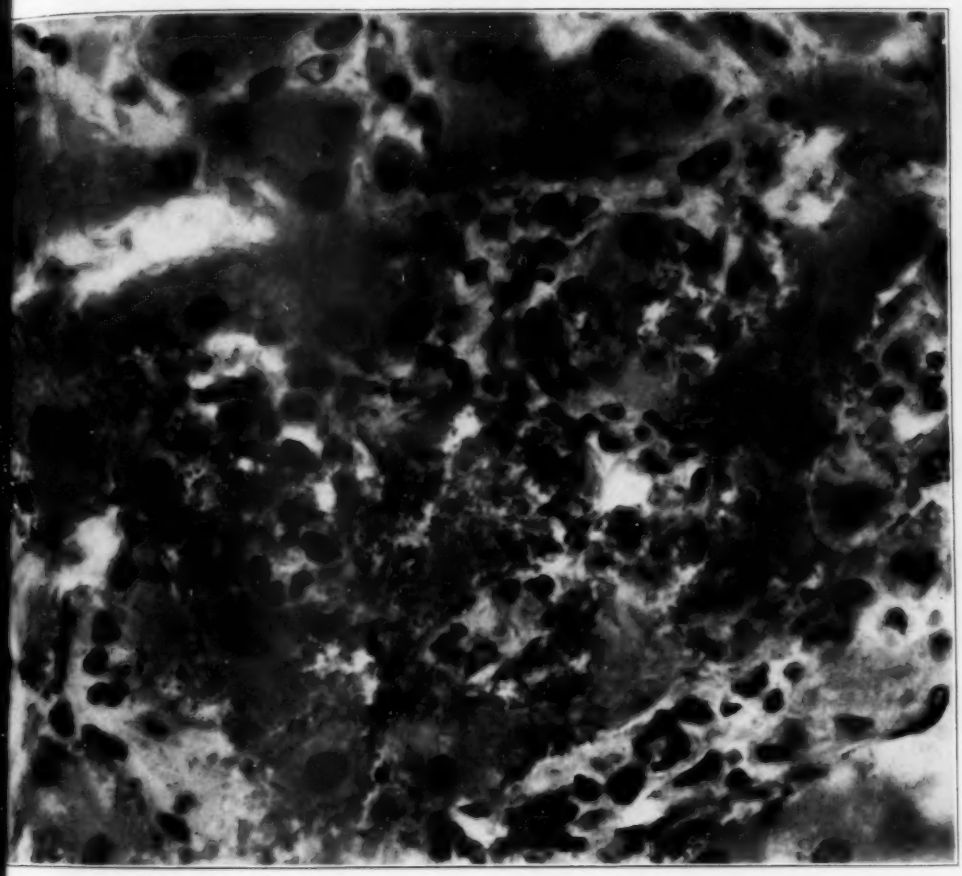

Fig. 4.—High power photomicrograph (oil immersion) showing the bacilli in the hepatic sinusoids and capillaries.

Pathologic Diagnosis.—This comprised: coronary sclerosis; atheromatosis of the aorta, with hemolytic staining of the intima; emphysema and bilateral chronic adhesive pleuritis; chronic periportal hepatitis; acute focal hepatitis with focal necrosis; acute catarrhal cholangeitis, and choledocholithiasis; acute and chronic ulcerative cholecystitis (presence of B. welchii) and cholelithiasis; septic softening of the spleen; surgical removal of the right kidney; pyelitis; local recurrent hypernephroma and compensatory hypertrophy of the left kidney.

Ten Reported Cases of Infection of the Gallbladder by B. Aerogenes Capsulatus

Author	Year	Sex	Age	History of Previous Attack	Interval of Well-Being Between Previous and Final Attack	Jaundice	Gallstones	Gangrene of Gallbladder Wall	Abscesses	Ulceration	Perforation	Outcome (Recovery or Death)
Cottam [10]	1917	F	41	None	.....	.....	Five small	Yes	.....	....	.....	Recovery
Halle and Marquézy [11]	1922	F	60	Sudden violent pain in right shoulder with vomiting	5 days	.....	None	Yes	.....	Yes	.....	Death
Leréboullet [12]	1922	..	..	.....	.....	.....	One	Yes	.....	....	Yes, with fetid pus	Death
Kirchmayr [13]	1925	M	64	Abdominal cramplike pain	14 days	No	Sand, with granules the size of hempseed	Yes	Multiple in wall	Yes	No	Rapid recovery
Gould and Whitby [14]	1927	F	46	No	.....	.....	Six	Yes	.....	Yes	.....	Recovery
Wahlberg [9]	1927	F	36	Severe pain below right costal arch	5 weeks	Slight	.....	....	.....	....	.....	Recovery
	1927	..	..	.....	.....	.....	.....	....	Yes	....	Yes	Recovery
Spitznagel [15]	1929	M	50	Sudden severe pain in region of gallbladder which subsided after a few hours	4 days	Intense	None	Yes	.....	Yes	.....	Death
Hegner [16]	1931	M	62	Pain like colic due to gallstone	16 days	Slight	.....	....	.....	....	.....	Death
Graef and Sturtevant	1933	M	63	None	.....	0	Numerous	Yes	Yes	Yes	.....	Death

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ANALYSIS

In 10 of the reported cases of infection of the gallbladder by B. aerogenes-capsulatus, including our own case, the ages were given in 8 cases, as follows: 36, 41, 46, 50, 60, 62, 63 and 64. The average age was 52.75. Four of the patients were women and 4 men.[17] In only 1 case was there a history of biliary disease. Five patients had a preliminary attack of pain like that of colic due to gallstones, which subsided. It was followed by a secondary attack ending rapidly in death or operation. The interval between the pain and the rapidly fulminating attack was four days, five days, fourteen days, sixteen days and five weeks. It has been suggested[18] that the preliminary attack is pain due to gallstones, and that at this time injury is done to the mucosa, making invasion by the gas bacillus possible. Opposed to this theory is the fact that Halle and Marquézy's patient had no gallstones with a typical prodromal attack. Of the 10 patients, 5 recovered and 5 died.

Our patient gave no history or signs of cholelithiasis, clinically, yet from the pathologic examination we are certain that there were biliary calculi, with chronic cholecystitis and probably chronic periportal hepatitis. The dilated duct and ampulla suggested that one stone at least had passed. In the absence of a history of this event, the suspicion arises that possibly some of the history may have been withheld. During the four days of observation the patient seemed like a person who is ill from beginning pneumonia or some severe infection, but there were no localizing symptoms.

SUMMARY

Nine cases of infection due to B. aerogenes-capsulatus of the gallbladder are collected, and 1 case is added. With or without a preliminary attack of pain and a quiescent period of from four days to five weeks, the patient is seized with an overwhelming infection, which usually points to involvement of the right upper quadrant. In 2 cases it was difficult to localize. Death quickly supervened when operative relief was not given quickly. The diagnosis in the authors' case was made post mortem.

17. In 2 cases neither age nor sex was reported.
18. Kirchmayr[13] and Wahlberg.[9]

ACUTE APPENDICITIS

A SECOND REPORT OF ONE THOUSAND CONSECUTIVE CASES

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One thousand consecutive cases of acute appendicitis were reported by myself and Dr. Waldschmidt in 1928.[1] From September, 1927, to October, 1932, a second series of one thousand patients with the same diagnosis have been operated on by the surgeons of the Quain and Ramstad Clinic.

In studying the records in this second series, we were confronted with the same difficulties which we met in our first report, namely, the impossibility of making an accurate classification of the stages or complications of the disease found at the time of operation without the use of a long and useless list of adjectival phrases. However, our report is intended chiefly for the practical surgeon who is more interested in the welfare of his individual patients than in the details of pathologic by-products and side issues which have no vital bearing on the success or failure of treatment.

While the former classification is continued, it is not claimed to be scientifically accurate; yet we believe that it serves a very practical purpose at the time of operation in helping the surgeon to decide the two vital questions, *whether* to drain and *how* to drain.

According to our method of classification, the plan is to place in group I all cases which do not need drainage. If a drain has been inserted as a precautionary measure and later developments (a sterile culture or the absence of a local reaction) indicate its early removal, the case would still belong in group I.

Since we follow, in general, the same surgical technic in the treatment of all patients in whom the infection has gone through the appendical wall, it seems superfluous to classify cases in groups II and III. Such a classification is merely an indication of the surgeon's best opinion

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An abstract of this article was presented before the Western Surgical Association, Madison, Wis., on Dec. 8, 1932.

1. Quain, E. P., and Waldschmidt, R. H.: Acute Appendicitis, Arch. Surg. **16**:868 (April) 1928. In order that the reader may fully understand the references to the former report which will be made in this article, it is advisable that he read the former report before he proceeds with the present discussion. A limited number of reprints are obtainable from the authors.

*Grouping of 1,000 Cases of Acute Appendicitis According to Extent of Peritoneal Infection**

	Group I	Group II	Group III
Total number of cases	637	212	151
Appendectomy performed	637	209	151
Appendectomy not performed	0	3	0
Died	2	9	27
Age of patients			
Youngest	2 years	2 years	21 months
Oldest	58 years	78 years	73 years
Average	22 years	21 years	19 years
Time of operation after onset			
Shortest	½ day	½ day	1 day
Longest	26 days	21 days	22 days
Average	3¼ days	4¾ days	4½ days
Duration of drainage			
Shortest	1 day	1 day	½ day
Longest	8 days	65 days	65 days
Average (of those drained)	2 days	14 days	16½ days

Major Postoperative Complications

Group I		Group II		Group III	
Secondary abdominal abscess	3	Secondary abdominal abscess	5	Secondary abdominal abscess	6
Acute bronchitis	1	Multiple abscess of liver	1	Subphrenic abscess	1
Coronary embolism	1	Pelvic abscess	2	Acute bronchitis	1
Enteritis	1	Subphrenic abscess	1	Empyema	1
Postoperative hemorrhage	1	Acute bronchitis	4	Enteritis	1
Intestinal obstruction	2	Pulmonary embolism	1	Fecal fistula	13
Acute otitis media	1	Fecal fistula	10	Postoperative hemorrhage	3
Acute parotitis	2	Postoperative hemorrhage	1	Influenza	2
Acute progressive peritonitis	1	Pulmonary infarct	1	Myocardial insufficiency	2
Phlebitis	1	Acute mania	1	Intestinal obstruction	31
Acute pleurisy	1	Myocardial insufficiency	1	Acute otitis media	2
Pneumonia	3	Acute nephrosis	1	Acute parotitis	1
Acute pyelitis	2	Intestinal obstruction	24	Phlebitis	1
Acute tonsillitis	2	Phlebitis	2	Pneumonia	4
Variola	2	Pneumonia	3	Acute pyelitis	1
		General septicemia	1	General septicemia	1
		Acute tonsillitis	1	Cerebral thrombosis	1
				Acute tonsillitis	2
				Acute uremia	1

Secondary Operations

Group I		Group II		Group III	
Enterostomy	5	Enterostomy (51 primary)	84	Enterostomy (92 primary)	129
Incision and drainage of abdominal abscess	3	Closure of fecal fistula	7	Closure of fecal fistula	6
		Incision and drainage of abdominal abscess	5	Incision and drainage of abdominal abscess	6
		Gastrostomy	2	Gastrostomy	6
		Drainage of pelvic abscess	1	Cecostomy	3
		Intestinal resection	1	Intestinal resection	2
				Thoracotomy	1
				Drainage of pelvic abscess	1
				Ileocolostomy	1

Mortality

Group I		Group II		Group III	
Coronary embolism	1	Multiple abscess of liver	1	Peritonitis and ileus	19
Enteritis and streptococcic peritonitis	1	Bronchopneumonia	1	Peritonitis and bronchopneumonia	4
	—	Pulmonary embolism	1	Peritonitis and diabetes	1
Total	2	Postoperative hemorrhage	1	Peritonitis and myocardial insufficiency	2
	(0.31%)	Ileus	3	General septicemia	1
		Ileus and acute mania	1		—
		General septicemia	1	Total	27
			—		(17.8%)
		Total	9		
			(4.2%)		

Average mortality in 1,000 cases	3.8 %
Average mortality in 2,000 cases now reported	3.25%

* Group I includes cases of infection confined to the appendix; group II, abscess, and cases with peritoneal infection restricted to the immediate neighborhood of the appendix (early stage of progressive peritonitis), and group III, cases of diffuse and progressive peritonitis.

after consideration of both the preoperative and the operative findings. It simply shows his judgment as to the degree and extent of infection at the time of operation. "Progressive" peritonitis is present on every peritoneum after contamination from a ruptured appendix. The "progress" may become limited by nature, by the surgeon or by both. The classification, although illogical, has been continued from force of habit rather than from need or from the point of view of practical service.

We are aware of certain criticisms of our previous résumé based on the fact that it did not include any pathologic reports indicating whether in the cases in question the condition was acute appendicitis. In reply, it may be stated that no case of appendicitis has been included in group I in either of the reports unless the appendix was so acutely infiltrated, thickened, distended or surrounded by recent adhesions, exudate or fibrinous deposits that any tyro in the profession could recognize it as the site of an acute infection.

Furthermore, in all the cases of appendicitis in group I (infection confined within the appendix) the appendix was sectioned and microscopically examined by a competent pathologist, and the acutely inflammatory process was verified. Cases of appendicitis usually classified as "interval (!)" were not included in either report.

In groups II and III (appendicitis with abscess or local or progressive peritonitis) microscopic sections were not made, as a rule, unless definite information was desired as to the nature and origin of the infection (tuberculosis, tumor, etc.). In the presence of a gangrenous or perforated appendix located in an abscess cavity or in free communication with an infected peritoneum, laboratory examinations are not needed as an aid in either diagnosis or treatment.

The purulent exudate produced by the colon bacillus is readily recognized by its odor. The patient's resistance, as a rule, is more likely to overcome the colon type of bacteria than the almost odorless staphylococcic and streptococcic infection. (This observation has given rise to an operating room saying to the effect that "the worse they smell, the sooner they're well.") In all doubtful cases laboratory examinations governed in determining whether free peritoneal exudate was dangerously infectious or not. In the presence of an apparently unperforated appendix with a seropurulent or fibrinous exudate cultures were always made. Smears were examined immediately, except at night, when laboratory attendants might not be available.

The method of operation was the same as that previously described. Enterostomy was performed more often than in the former series. In some cases the results were disappointing. More often it gave satisfaction, and many times it was so evidently life-saving that we do not feel justified in limiting its use, in spite of the critical attitude adopted by some eminent surgeons.

The earliest possible removal of an acutely inflamed appendix, irrespective of its "classification," seems as essential now as before. The same holds true in regard to the necessity of locating and delivering the appendix by finger touch and with the least possible retraction and disturbance of the intra-abdominal contents.

The importance of constant and experienced postoperative management may be seen in the following comparison between the mortality in the two hospitals where our patients were treated. Of the 323 patients operated on for acute appendicitis in hospital no. 1, 16 (4.9 per cent) died, while in hospital no. 2, 22 (3.2 per cent) deaths followed the same type of operation on 677 patients. There was no appreciable difference in the severity of the disease among the patients admitted to the two hospitals. The postoperative observation and treatment in hospital no. 2 are under the direction of one man, an associate surgeon of twenty years' experience, who has made a special study of the type of complications usually met with in this disease.

We can find no other reason for the decidedly higher mortality in the second series than the longer time which elapsed between the onset of the illness and the operation. Our records show that the average time between the onset and operation was more than twelve hours longer in the second series than in the first. This fact may largely be ascribed to the hard times and to a universal tendency to "wait and see" before deciding to incur the expense of medical care. In the meanwhile, various family remedies, including laxatives in liberal doses, have served to disseminate the infection.

Two patients who were admitted to the clinic with a diagnosis of acute appendicitis were in extremis and were not operated on. Several patients with severe peritonitis died within a few hours after operation.

The case histories were studied thoroughly, and the postoperative results are shown in the table, which was arranged as nearly as possible in conformity with the previous report.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomaly.—Roscher [1] reviewed malformations observed in the Norwegian University Clinic from 1914 to 1930. The material is divided into two groups: (1) cases in newly born infants (1,532 necropsies, which revealed 104 malformations, of which 40 were malformations of the kidney or urinary tract) and (2) cases in older children and in adults (3,995 necropsies, in which 104 malformations of the kidney or urinary tract were discovered).

Hydronephrosis and anomalies of the ureter were common in the first group and were associated with stricture, valvular formation and dilatation of the ureter. The author stated, however, that he found hydronephrosis and dilatation of the ureter without any associated stricture or valvular formation. It is evident from the material that hydronephrosis and dilatation of the ureter should be regarded as malformations and not merely as secondary results of stricture.

Roscher found that 9 of 11 cases of cystic kidney were associated with malformations in the urinary tract or elsewhere; this clearly indicates that cystic kidney, or at least its origin, is a malformation. In the second group, aplasia and hypoplasia of one kidney occurred in 0.75 per cent of the cases. About 50 per cent of the cases of hypoplasia were associated with hydronephrosis. The hydronephrosis was unilateral in

1. Roscher, Fredrik: Ueber die Häufigkeit, die Art und die pathogene Bedeutung von Missbildungen der Niere und der Harnwege, Acta chir. Scandinav. **70**:493, 1933.

14 instances and bilateral in 14. It was generally associated with malformations of the ureter, such as dilatations and valvular formations; the latter, however, usually did not occasion true obstruction. Of the 28 cases in which hydronephrosis was found, 19 were cases of pyelonephritis and 1 a case of pyelitis. In 12 cases the pyelonephritis was the direct cause of death and in 5 cases it contributed to a fatal issue. In only 2 cases had calculi formed. In the 12 fatal cases of pyelonephritis 8 of the patients were children under 7 years of age. These children had had pyuria for a long time, and most of them died in uremia.

Cystic kidney occurred bilaterally in 7 cases and unilaterally in 2. In 1 of the latter cases hydronephrosis was present in the opposite kidney. In the other case there was aplasia of the opposite kidney.

Settergren [2] gave an account of congenital ectopia of the kidney. He stated that the symptoms vary greatly and are not specific; consequently the diagnosis as a rule causes difficulty, particularly in cases of pelvic kidney in women. Pyelography generally clinches the diagnosis. A sound ectopic kidney that does not give rise to symptoms should be let alone, whereas a diseased kidney should be removed. When a sound kidney on account of its abnormal position produces symptoms or when a kidney presents pathologic changes without an unfavorable prognosis, nephropexy should be tried.

Settergren described 6 cases of abnormal position of the kidney, in 3 of which the condition was certainly congenital and in 3 of which it was probably congenital. In 4 of the cases the ectopia was on the right side, and in 2, on the left. Five of the patients were women, and 1 was a man. In cases 1 and 2 the diagnosis was made only after exploratory laparotomy performed because an ovarian tumor was suspected. In case 1, the kidney was situated in the small pelvis, and since nephropexy could not be carried out nephrectomy was done on account of pain, although the kidney appeared to function normally. It presented interesting anomalies in respect to its rotatory position and vascular supply. The patient's complaints disappeared after operation. In case 2, the kidney was situated immediately above the innominate line. The patient was three months pregnant. The kidney was retained, and pregnancy and parturition proceeded in a normal manner. In case 3, on pyelography, a probably ectopic kidney was noted, situated mainly above and close to the side of the sacral promontory. The patient had earlier passed through two parturitions without any particular difficulty. The renal symptoms were so slight that operation was not indicated. In case 4, operation was not performed. The patient was a nullipara,

2. Settergen, Folke: Ectopia renis congenita, Acta chir. Scandinav. **70**:563, 1933.

aged 74. A diagnosis of congenital pelvic kidney was made by means of pyelography. In case 5, in which the patient was a multipara, the ectopic kidney, situated above the small pelvis, had occasioned severe symptoms of cystopyelitis for fifteen years. The renal pelvis was transformed into a large, convoluted, saccular formation filled with concretions. The patient had earlier been treated for salpingitis, but the symptoms might even then have been caused by the unsound kidney alone. A roentgenographic shadow, probably occasioned by an atypical lobe of the liver, made the diagnosis more difficult. Nephrectomy was performed. In case 6, the ectopic kidney was pyonephrotic and contained concretions. Ureteral stricture may possibly have contributed to the renal complications. The diagnosis was made with the aid of a pyelogram; nephrectomy was performed, and typical vascular anomalies were found.

Settergren gave a final account of the relation of ectopia of the kidney to pregnancy and parturition. Considering the risk of complications that may thus arise, the lines of treatment are as follows: If from the obstetric standpoint operation on a sound ectopic kidney is considered to be indicated, nephropexy should be tried, and extirpation should be carried out only in absolutely imperative and exceptional cases. At parturition the patient with an ectopic kidney should always be hospitalized, even if delivery has occurred spontaneously earlier. In cases in which an ectopic kidney is present with simultaneous renal disease, there may sometimes be indications for sterilization. A ptotic kidney which is in an acquired anomalous position constitutes, as a rule, no complication in pregnancy or parturition.

Stone.—Hellstrom[3] reported recurrence of stones following their removal or passage from the upper part of the urinary tract. In 147 cases operation was not performed. In 108 cases the stone was passed, and there was no recurrence. In 14 cases the stone was not removed, but no additional stones formed. In 25 cases (17 per cent) new stones formed. In 8 of the cases in which there were recurrences the stone formed on the same side; in 8, on the opposite side, and in 7, on both sides. In 2 of the cases, the site of formation was not stated. Recurrence was looked for in 233 cases in which operation was performed. In 58 (25 per cent), there was recurrence. There was a true recurrence on the same side in 19 cases, and on both sides in 7. In 12 cases, stones recurred only on the side on which operation was not performed. In 4 cases, it was impossible to state the site of recurrence. In 16 cases stones developed as a result of fragments that were left

3. Hellstrom, John: Ueber Rezidive nach Operationen wegen Nieren-und Uretersteinen, Ztschr. f. urol. Chir. **37**:83 (April 22) 1933.

after operation. In 11 of these 16 cases multiple stones were known to be present originally; in 3 cases there was a large coralliform stone, and in 2, extensive infection was present.

Pyelolithotomy was performed in 5 cases, pyelonephrolithotomy in 3 and nephrolithotomy in 6; pyelo-ureterolithotomy and ureterolithotomy were each performed in 1 case. In 3 of the cases in which operation was performed there was extensive bilateral infection, and in 4 there were multiple oxalate stones. In 19 cases the stone recurred only on the side on which operation was performed; in 7 it recurred on the opposite side. Therefore, stones recurred in 26 cases (11 per cent). In 13 of the 26 cases of true recurrence (50 per cent), the stones formed in the first three years after operation. In 15 of these 26 cases, pyelolithotomy had been performed; in 5, nephrolithotomy, and in 6, ureterolithotomy. In 12 cases stones recurred only on the side on which operation was not performed.

Jasienski [4] reported an unusual case of renal stone of a type not hitherto mentioned in the literature. A man, aged 44 fell 4 meters (about 14 feet) a few years previous to observation; this was followed by crises of pain at various times, accompanied by hematuria. Roentgen examination disclosed multiple calculi extending into the subcapsular bed of each kidney. After several weeks, during which progressive anemia developed, right lumbotomy was done; the kidney was incised down its entire length, and the calculi were removed. One week later the patient's condition was so grave because of continuous hematuria and anemia that it seemed necessary to remove the right kidney, although the condition of the left kidney forbade it. The patient died the following day. At necropsy the left kidney was found to be small and full of stones but not otherwise diseased. In the right kidney, both the cortex and the medulla and also the calices contained a great number of irregular spaces varying from the size of a pinhead to that of a hazelnut, which were lined with crystalline concretions, in some places amorphous and in others exhibiting a granular structure. Histologic examination revealed that in the midst of very hard crystalline concretions were fibrinous masses and depigmented red corpuscles, encircled with concretions. Chemical analysis disclosed that these masses were composed almost half of albumin, probably fibrin, which was impregnated with calcium phosphate and contained some calcium oxalate. There was no evidence of any other constituents.

The anatomic lesions observed in the kidney probably explain the action of the concretions for a long time on the renal parenchyma. The inflammatory changes corresponded to the "lithiasic nephritis" of

4. Jasienski, George: Sur un cas rare de lithiase rénale bilatérale, J. d'urol. **34**:408 (Nov.) 1932.

Albarran. The numerous signs of cirrhosis and cicatricial changes, followed by great shrinkage in size, justified a diagnosis of cirrhotic lithiasis (Israel). The hematin composition revealed that the production of calculi was due to the renal hemorrhages. Around the clots were incrustations of urinary salts, following the course of the modified surface and constituting the mold for the stones. The absence of infection also showed that the calculi were due solely to hemorrhage. It is possible that there had been acute hemorrhagic nephritis.

Tumor.—Fischer [5] reported 48 cases of tumor of the kidney and of the renal pelvis. Thirty-five patients were operated on, and 6 refused to undergo operation. In 3 cases, exploratory incision showed that removal was impossible; in 2 of the remaining 4 cases, the general condition would not permit operation, and in the other 2, metastases to the bones and lungs were present. Histologic investigation revealed that typical or atypical hypernephroma was present in 29 cases. In 4 cases the condition was diagnosed as carcinoma, and in 4 others papilloma of the renal pelvis was present. In another case, that of a child aged 5 years, an adenosarcoma was present. The primary mortality in the cases in which operation was performed was 17 per cent; 3 patients died of myocardial weakness, 1 of shock resulting from the operation, 1 of pneumonia and 1 of uremia. In 13 of the 24 cases in which data were obtained there was local recurrence after the operation. Recurrence and metastasis occur most commonly in the first three years after operation. After that they are rare.

Harrah [6] stated that progressive enlargement of the abdomen of an infant or a young child should be looked on with grave suspicion. Malignant tumor of the kidney in infancy and childhood is not extremely rare. In many cases the enlargement of the abdomen is the only symptom for a long time. Absence of pain and hematuria, particularly the latter, early in the growth of the tumor is unfortunate from the standpoint of early diagnosis. The absence or late appearance of hematuria in cases of renal tumor of children may be connected with the growth capacity of the young kidney, which enables its structures to keep pace with the growth of the tumor and thus to preserve their continuity for a long time.

Harrah stated that the prognosis when these tumors are present is very serious. The best prospects, in his opinion, lie in a combination of radiotherapy and surgery. Because of the "silent" nature of the tumor in many cases, regional invasions and metastasis are likely to be present by the time the urologist or the surgeon first sees the patient.

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5. Fischer, Karl: Ueber Neubildungen der Niere und des Nierenbeckens, Ztschr. f. urol. Chir. **37**:16 (April 22) 1933.

6. Harrah, F. W.: Embryonal Sarcoma of the Kidney in Children, J. Urol. **29**:445 (April) 1933.

Lipomatosis.—Young [7] described 11 cases of fatty invasion of the kidney, or replacement lipomatosis. In the first case, invasion occurred in the absence of infection, pyuria and nephrolithiasis. Although there was no evidence of infection within the kidney, there was slight evidence of perinephritis associated with the fatty invasion in all the cases. In all the cases there was an increase in the amount of perirenal fat, which was firmer than normal and surrounded the pelvis, entering the hilus around the vessels and the pelvis and following the infundibula into the kidney. The pelvis was always embedded in fat, and in some cases it was obliterated. The fat evidently invades the kidney, carrying fibrous tissue membrane before it, filling in preexisting spaces, invading the space between the cortex and the infundibula and calices and, when hydronephrosis is present, surrounding and compressing this until complete obliteration has occurred in some places. In 2 cases in which the condition was not associated with lithiasis, atrophy of the kidney had gone on to a remarkable degree.

Young stated that replacement lipomatosis is related to the process commonly known as autonephrectomy. Most extensive fatty invasion has occurred in completely obstructed kidneys. Atrophy of renal substance might be secondary to replacement by fat and the consequent cutting off of the blood supply. Replacement lipomatosis becomes important clinically, since this condition has been mistaken for a renal neoplasm. It may account for enlargement of the kidneys in cases of obstruction of the upper part of the urinary tract with or without the presence of stones. A different process in this condition, however, would lead to atrophy of a kidney and autonephrectomy.

Young stated the belief that true lipomas are rare; they are usually small and yellowish and are found as nodules encapsulated by fibrous tissue in the cortical layer distinctly beneath the kidney capsule. They result from rests of fatty tissue which have become included in the kidney during embryonic life. Replacement lipomatosis possesses none of these characteristics.

Krymholz [8] stated that atrophy of the kidney with substitution by fat, so-called lipomatosis perinephritis, is rarely observed. This should not be confused with a fatty tumor (lipoma) of the kidney or of its capsule. In the center of the fatty tissue, pus or a stone may frequently be found. The fatty substance of atrophic kidneys is not always firmly adherent around the stone; in some cases roughness of the stone or

7. Young, H. H.: Lipomatosis or Destructive Fat Replacement of the Renal Cortex, J. Urol. **29**:631 (June) 1933.

8. Krymholz, M.: Zur Fettsubstitution der atropischen Niere, Ztschr. f. urol. Chir. **36**:343 (March 11) 1933.

spurs are not found; that is, the stone is free in the substance. Fatty changes of the kidney as well as fatty substitution in the atrophic kidney may also be associated with tuberculosis.

Krymholz expressed the belief that renal atrophy and substitution by fat result from a disturbance of the blood supply of the organ; later inflammation of the solid substance of the kidney and hyperplasia result from irritation. The general process of replacement by fat is carried on by long drawn out, chronic infection of low degree.

Cysts.—Blum [9] reported a case of echinococcic cyst of the kidney in a man. Examination revealed one small cyst coming down from the ureter. The patient had passed cysts with the urine for a number of years. Nephrectomy was satisfactorily performed.

Blum stated that 40 per cent of the reported cases of this kind have occurred among workers who handled pigs and cattle. Another source of infection is pets that have access to slaughter-house material. Children become infected through contact with pets, and adults through contact with the children.

Tuberculosis.—Salleras [10] stated that although pyelography reveals nothing of value in the initial stages of renal tuberculosis, it is possible later to make a diagnosis by means of pyelography alone even in the absence of all other characteristic signs, such as the presence of the Koch bacillus, Colombino's sign, a decrease in the amount of urea and decisive cystoscopic signs. One need not wait to learn the results of inoculation of guinea-pigs. The pyelographic evidences of renal tuberculosis may be summarized as follows: The lesions begin in the renal papilla and advance progressively. This advance appears in the form of hollow pouches which increase in size with the age of the process, the same image, as well as the identical form, being repeated with equal clearness in all cases, thus making the picture characteristic. By this means Salleras was able to establish: (1) whether the condition is tuberculous pyonephrosis or some other form of pyonephrosis; (2) whether the disease is in the initial or in an advanced stage; (3) whether it is unilateral or bilateral and, if the latter, which kidney exhibits the greater destruction, and (4) whether there is transmission of the renal process to adjoining organs.

The differential diagnosis is based essentially on the fact that in nontuberculous pyonephrosis the dilatation begins in the ureter or pelvis and is then transmitted to the renal parenchyma, finally assuming the

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9. Blum, Viktor: Ueber Nierenechinococcus, Ztschr. f. urol. Chir. **37**:46 (April 22) 1933.

10. Salleras, Juan: Valor de la radiografía simple en la localización de la tuberculosis renal y de la pielografía en el diagnostico de la misma, Bol. y trab. de la Soc. de cir. de Buenos Aires **16**:1216 (Oct. 26) 1932.

appearance of a single large cavity. In tuberculous pyonephrosis, on the contrary, both the ureter and the renal pelvis preserve their shape, the cavity at the level of the renal papilla beginning late and extending thence in an eccentric and shaggy form, by ulceration, to the cortex, as may be seen in the pictures included in the original article.

It is possible, accordingly, in a tuberculous kidney, to follow step by step the distinct phases of ulceration, from simple clouding of the outline of the corresponding calix to deep ulceration and even, in exceptional cases, to ulceration of an adjoining organ (intestine). In other words, pyelography serves to measure the anatomic value of the tuberculous kidney.

Tuberculosis of one or of both kidneys is then easy to recognize by the clear and regular outline of the papillary portion of a sound organ or by the eroded, shaggy and distorted appearance of the papilla and cortex if the kidney is diseased. The diagnosis of unilaterality or bilaterality of the papillary lesions can then be made, and in the latter case, it can be determined which side is more severely affected. The extent of injury to the kidney that has been partially destroyed by caseation can also be measured; bilateral pyelograms are an interesting guide in the decision for or against nephrectomy.

When the lesions have invaded the perirenal tissues or a nearby organ, the pyelographic images faithfully record such invasions by exhibiting shadows and distortions which, starting from the renal papilla, extend to the corresponding perirenal zone or establish communications with adjacent organs.

The use of excretory pyelography with iopax or skiodan, although satisfactory in some cases in which retrograde pyelography cannot be carried out, gives rather uncertain images, for although it produces fair shadows of cavernous lesions, the impossibility of basing a diagnosis on these is admitted. The relation between the elimination of opaque products and the quantity of renal parenchyma teaches that in the greater lesions there is less excretion than is needed to fill such ulcerations sufficiently to make them recognizable.

[COMPILERS' NOTE.—There is no doubt that it is possible by roentgenography alone to diagnose well advanced renal tuberculosis in which caseation of the organ is the predominant feature, as in certain cases of occluded renal tuberculosis or of closed tuberculous pyonephrosis which have been recorded in the literature as instances of autonephrectomy. Pyelography beyond question is one of the greatest advances for establishing a correct diagnosis of renal tuberculosis, as well as of any other lesion of the kidney. The indications for nephrectomy, however, should be based on the diminution of function of the organ with reference to elimination of urea or excretion of phenol-

sulphonphthalein, on the presence of the Koch bacillus in the catheterized specimen and on a positive pyelogram. This triad of clinical data is essential for reaching a definite diagnosis, since the presence of the bacilli of tuberculosis in the excreted urine does not always mean surgical renal tuberculosis.[11]

Rupture of a pyonephrotic tuberculous kidney, leading to a perinephritic abscess and then to a renocolic or a nephrobronchial fistula, although rare, has been recorded in the literature in several instances. Crenshaw [12] recently reported 2 cases of pyonephrosis with nephrobronchial fistula observed in a series of 256 cases of perinephritic abscess.

It is obvious that although intravenous pyelography, as Salleras stated, will not always solve the problem of the diagnosis of renal tuberculosis, it is of definite value in cases in which catheterization of the ureters cannot be accomplished and also in early lesions of the medullary or cortical renal substance, which have no connection with the excretory apparatus of the organ.]

Saenz and Eisendrath,[13] in the course of studies of the respective sensibility of methods of direct culture of the bacillus of tuberculosis, observed that performing "raclage" (harvesting or scraping together several cultures) of the tubes that had been sown with suspected material before any macroscopically visible culture appeared was of great advantage as a practical means of establishing an early diagnosis. They accordingly reported the results of a bacteriologic and clinical study of 57 cases in which renal tuberculosis was suspected. By a special technic they succeeded in isolating the bacillus of tuberculosis. In 30 specimens of urine the result was positive, and in 27 it was negative. Of the 30 cases in which the results were positive, 20 showed the bacilli on direct examination. After culturing, it was possible by means of "raclage" of the tubes to discover microcultures of acid-fast bacilli in the 30 positive cultures after eight to thirty days (in most instances within ten days), whereas the macrocultures did not appear until after from fifteen to sixty days. It was thus clear that a diagnosis could be made by their microculture method in half the time required for macroculture. It is worthy of note that in the 57 cases the results of direct examination, carried out simultaneously at the Pasteur

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11. Gutierrez, Robert: Nonsurgical Renal Tuberculosis, Am. J. Surg. **5**:99, 1928; Diagnostic et traitement chirurgical de la tuberculose rénale, J. d'urol. **31**:126 (Feb.) 1931.

12. Crenshaw, J. L.: Pyonephrosis with Nephrobronchial Fistula, J. Urol. **28**:427 (Oct.) 1932.

13. Saenz, A., and Eisendrath, D.: La "microculture" et son importance dans le diagnostic précoce de la tuberculose rénale par l'ensemencement des urines, Presse méd. **40**:1856 (Dec. 10) 1932.

Institute and at the Necker Hospital, agreed in every respect. One interesting urologic discovery was the close relationship between the elimination of the bacilli of tuberculosis and the pathologic lesions of the patient. When the case is one of renal tuberculosis in which the focus is almost excluded, that is, when the renal pelvis is very small, bacilli of tuberculosis are found only intermittently. The study also revealed that bacilluria persists much longer after nephrectomy than has been supposed. In most cases, it disappears within the first six months following the operation, except when there is unsuspected bilateral infection. In 4 cases in which the patients were examined, two, four, five and six years, respectively, after nephrectomy, the culture was still positive. This shows that cultures should be made more often for the study of such postoperative signs as frequency of urination and cloudy urine.

From this study it becomes clear that it is unsafe to remain content with the result of direct culture alone, for this will be insufficient in 25 per cent of the cases. It is indispensable to culture the sediment of from 20 to 50 cc. of urine on from six to eight tubes of medium prepared according to the special technic described by Saenz and Eisendrath, and especially to examine systematically the product of "raclage" of every tube from the eighth day on. In this way an early precise diagnosis may be made in many cases in which direct examination of the sediment gives negative results. This method is more rapid and more reliable than inoculation of guinea-pigs. It has the advantage of permitting isolation of acid-fast bacilli (avian, paratuberculosis) that are nonpathogenic for the guinea-pig, and it also permits immediate identification of human or bovine types. The simplicity and ease of the method and the accuracy of the results make its use desirable in the future in the diagnosis of renal tuberculosis.

[COMPILERS' NOTE.—It is gratifying that a new routine procedure for the detection of the bacillus of tuberculosis has been established. The method described appears to be more accurate than inoculation of guinea-pigs, culturing on potato mediums and routine examination of smears, methods so commonly in use. It is also of interest that the Necker school [14] has again brought to light a well known phenomenon clearly described years ago by Albarran,[15] namely, the frequent finding of the bacilli of tuberculosis in the urine excreted by the sound kidney, even a long time after nephrectomy.]

14. **Motz, Charles**: Les pyonéphrites. Arch. urol. de la Clin. de Necker **7**:222 (Nov.) 1932.

15. **Albarran, J.**: Lésions du rein du coté opposé dans la tuberculose rénale unilatérale, Ann. d. mal. d. org. génito-urin. **26**:81, 1908.

Hydronephrosis.—Walters,[16] in a consideration of the conservative treatment of hydronephrosis, stated that if the renal parenchyma is functioning normally enough, removal of the obstructing factors which produce the hydronephrosis should give relief from the obstructive symptoms, and the pelvis and calices should return to within reasonably normal limits of size. In his experience, resection of the hydronephrotic renal pelvis gives excellent results in the treatment of hydronephrosis in properly selected cases. Ureteropyeloneostomy has relieved for almost four years hydronephrosis of a solitary kidney in which obstruction was complete at the time of operation.

Walters stated that if a surgeon chooses to reimplant the ureter into the dependent part of the renal pelvis, accurate anastomosis should be made between the cut end of the ureter and the opening in the pelvis, for any redundant portion of the ureter extending into the pelvis may serve as an obstructing valve. He stated that conservative procedures, such as resection of the renal pelvis, reimplantation of the ureter and removal of such obstructions as peripelvic tissue, are most strikingly indicated when the hydronephrosis is bilateral or when it is unilateral but sufficient renal parenchyma remains to justify the preservation of the organ. The necessity for the use of conservative procedures for the relief of obstruction when the kidney is solitary is apparent. In making the decision as to the best conservative procedure to follow, the guide is the surgeon's own experience, it being remembered that the safest and the best procedure is that which produces adequate and complete relief of the obstruction with minimal disturbance of the renal pelvis and the ureteral tissues.

Young[17] stated that the trend of surgery is more and more toward conservatism in the treatment of renal diseases, particularly hydronephrosis. It used to be thought that when a kidney was functionless or badly infected or had a greatly dilated pelvis nephrectomy was indicated. Physicians did not realize that by good drainage such kidneys can be brought back almost to a normal condition and the infection eradicated. Young recently observed a case in which there was a hydronephrotic sac which held about 4,000 cc. The fluid within it was thickly purulent, and there was no renal function, as revealed by the phenolsulphonphthalein test. The use of an indwelling ureteral catheter after a few weeks brought this apparently completely destroyed kidney back to equality with that on the opposite side. At operation, in which the obstruction was found to be due to a vascular cord, Young was able

16. Walters, Waltman: The Conservative Treatment of Hydronephrosis by Resections of the Renal Pelvis and Other Plastic Operations, J. Urol. **29**:121 (Feb.) 1933.

17. Young, H. H.: Discussion of Kidney Surgery, J. Urol. **29**:148 (Feb.) 1933.

by a new technic to remove the ureter from propinquity to the vascular cord by anterior and posterior plastic operations and to obtain a cure without either dividing the cord or transplanting the ureter. Since that time this technic has been carried out in several cases by Young and his associates with equally good results; the author feels certain that in cases of hydronephrosis produced by vascular cords compressing the ureter at its juncture with the pelvis, this operation will give good drainage of the pelvis and cure the hydronephrosis.

Rupture.—Ewell [18] stated that traumatic rupture of a hydronephrotic kidney, although rare, should be borne in mind if renal injury is suspected, as its presence may alter the operative treatment in a given case. Cases in which rupture of the kidney in children is suspected as a result of mild trauma are usually cases of hydronephrotic kidney. The symptoms are more variable in cases of rupture of hydronephrotic kidneys than in cases in which the kidneys are normal. Primary nephrectomy is the treatment of choice; however, in the light of knowledge of the surgical treatment of hydronephrosis, it may be possible in some cases to perform a conservative operation.

Aneurysm.—Gerard,[19] on the basis of 61 cases recorded in the literature as instances of aneurysm of the renal arteries (49 true and 12 false), repudiated the idea that any but true aneurysms exist, stating that the so-called false aneurysms are merely complications of renal contusions. The old classification of traumatic and spontaneous aneurysms must also be discarded as unsound. The symptomatologic triad of pain, hematuria and perirenal swelling, classically accepted, is accordingly false, being founded on a nonexistent basis, since it was found in only 5 cases (10 per cent). Aneurysms of the renal arteries are equally common in males and in females and in the right and in the left artery. They are almost always unilateral and solitary. They are almost always situated outside of the renal parenchyma and in the immediate vicinity of the hilus or internal to it, most often in intimate connection with the renal pelvis.

Nonruptured aneurysms develop in aged persons and are chiefly due to arteriosclerosis. They have a tendency to exhibit calcification. Clinically, they are manifested by pain in the region in which they are situated. When they are calcified, roentgen examination may reveal an "annular shadow," which is localized by pyelography at the hilus but outside the renal pelvis, thus making precise diagnosis possible.

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18. Ewell, G. N.: Traumatic Rupture of a Hydronephrotic Kidney, J. Urol. **29**:685 (June) 1933.

19. Gerard, Maurice: Les aneurysmes des artères rénales, J. d'urol. **34**:353 (Nov.) 1932.

Renal aneurysms that rupture develop as a result of the ordinary causes producing all aneurysms. They occur most often in young persons and produce no clinical manifestations, their course being insidious and their existence unsuspected up to the critical moment when they rupture. The prognosis in these cases is very grave. These aneurysms are a third more common than the nonruptured type. Rupture may be present in three clinical forms: 1. A pure hematuric form (33 per cent), with pain in the zone comprised. This type is difficult to diagnose by the common urologic methods; arteriography may be of assistance. 2. A form with perirenal tumefaction, which is more common (almost 50 per cent of cases). There are cataclysmic symptoms, a large perirenal collection of blood and a sensation of pain and pressure. Accurate diagnosis is almost impossible. The course is rapid, and the prognosis, grave. 3. A mixed form (rare), which is also very grave.

Treatment is always surgical. Gerard stated that treatment of nonruptured aneurysms has been attempted 5 times: in 4 cases of nephrectomy, and in 1 case by removal of the saccular aneurysm, with suture of the hiatus and conservation of the kidney. A cure was obtained in all the cases, but all occurred relatively recently. In the 29 known cases of ruptured aneurysm, 16 operations have been done: 3 between 1900 and 1906, and the others since 1914. In 4 cases the operations resulted fatally: Pinkert's case (laparotomy for occlusion by perirenal hematoma); Chisholm's case (exploratory laparotomy for perirenal hematoma); Janssen's case (exploratory lumbotomy followed by fulminating rupture of the aneurysm), and Hinman and Olson's case (nephrectomy). In the other 12 cases, in all of which nephrectomy was performed, the operations were followed by cure. Orth, in 1919, succeeded in removing the aneurysmal sac and in conserving a kidney with good function. This shows an interesting percentage (41.7) of cures attributable solely to operation.

In cases of calcified aneurysms, Gerard stated that good sense should dictate whether or not to operate, as in other conditions in aged or arteriosclerotic persons. In all cases of ruptured aneurysms, operation is imperative. With the pure hematuric form, there is plenty of time for all the necessary urologic examinations, but with perirenal hematoma and the mixed form, operation is practically always essential and delay cannot be risked. If it is in any way possible, however, the functional value of the two kidneys should first be determined. Lumbar nephrectomy is almost always the operation indicated for both ruptured and nonruptured forms. The pedicle should always be clamped promptly as a precaution against hemorrhage as a result of rupture of the aneurysmal sac during operation.

Decapsulation.—Putzu,[20] starting with the well known fact that the kidney is one of the organs regulating the acid-base equilibrium of the blood, undertook to see whether decapsulation caused any disturbance of this function. He made two series of experiments on dogs of medium size. In the first series, after testing the alkaline reserve of the blood, he decapsulated one kidney and then made tests twenty-four, forty-eight and seventy-two hours and five, eight, twelve, eighteen, twenty-five and thirty days after the operation. After a lapse of one month, he decapsulated the other kidney and performed the same tests before and after operation, at the same intervals. In the second series, he performed bilateral decapsulation in a single stage and made the same tests of the alkaline reserve and also tests of the renal secretory function.

In all cases the operation at first caused displacement of the equilibrium in an acid, never in an alkaline, direction. This began after twenty-four hours and increased up to the fifth day; it then decreased from the eighth to the twelfth day, reaching the original level between the eighteenth and the twenty-fifth day. In 2 cases, in which the operative trauma was greater, the original level was not reached until the thirtieth day.

As a result of these experiments, Putzu concluded that decapsulation does not produce any important or permanent disturbance of the acid-base equilibrium, and that, therefore, from this point of view the operation is almost devoid of danger.

Resection.—Mastrosimone [21] studied experimentally the comparative results of simple resection and suture of the solitary kidney and of resection followed by the implantation on the resected surface of a fresh autoplastic graft composed of a section, 1 cm. thick, of renal tissue which had a moment before been continuous with that surface. His study was particularly concerned with hemostasis, with the final fate of the implant itself and with the nature of any changes in renal function that might occur. He found that renal resection followed by the use of an autoplastic graft secures complete hemostasis and is always available, whereas resection followed by simple suture is not without danger of hemorrhage (secondary and late) and is not always feasible, since the piece of renal substance removed must be wedge-shaped if one is to produce a breach that can be sutured. When the former method is used, intravascular thrombosis is produced on the cut surface of the kidney, a consolidation of the vessel content which

20. Putzu, F.: L'influenza della decapsulazione renale sulla riserva alcalina del sangue, Arch. ital. di urol. **10**:40 (Jan.) 1933.

21. Mastrosimone, C.: Resezione ed innesto autoplastico sul rene unico, Ann. ital. di chir. **11**:2226, 1932.

naturally affords it protection and also helps the graft to adapt itself. The tissues on both surfaces being the same, the capacity for coagulation develops more rapidly, and the hemorrhage that immediately follows resection disappears rapidly and completely instead of slowly and tediously as when simple suture is performed.

Although certain phenomena of necrobiosis and partial substitution of connective tissue occur in the graft, this process is so gradual that it does no harm. The renal function is maintained in equilibrium and reveals no changes sufficient to contraindicate the method. On the contrary, the presence of the graft appears to produce a greater and more rapid compensatory hypertrophy which stimulates better function in the part of the kidney that remains than is observed when the kidney is resected and repaired with simple suture.

Hypertrophy.—Calef [22] carried out studies on dogs for the purpose of discovering what histologic and functional modifications occur in the kidney remaining in situ after removal of the opposite kidney. He found that there are never any histologic lesions suggesting degeneration or proliferation of the parenchyma, but merely compensatory hypertrophy as a result of increased work and hyperplasia of the cells of the tubules and the glomeruli. Therefore, no increase in the number of renal elements was noted. The size of the glomeruli in particular was greatly increased for a certain time after operation, but it returned to normal later. The hyperplasia also seemed to present regressive phenomena after two weeks.

The compensatory hypertrophy in the dog is not permanent but lasts only until the renal elements are in a condition to exercise their entire function. When perfect function of the cells is attained and when their reserve energies enter into harmonious activity, the kidney regains both macroscopically (in weight and size) and histologically (in the appearance of the tubules and the glomeruli) the appearance that it had before operation.

In experimental animals the renal function may return to normal after four or five days. In a series of 13 human beings studied, seven or eight days were required if the removed kidney had been functioning well, but function returned almost at once if the removed kidney had been greatly changed. In man a period of polyuria follows the return of normal function, but this was never observed in animals. The author concluded that, regardless of whether or not the extirpated kidney has been functioning well or ill, the kidney left in situ is capable of carrying on the uropoietic function perfectly, histologic degenerative changes or excretion in the urine of pathologic substances never having been noted, either in human beings or in animals.

22. Calef, Carlo: Modificazioni istologiche e funzionali del rene superstite dopo nefrectomia unilaterale, Arch. ital. di urol. **9**:575 (Dec.) 1932.

Surgical Technic.—Beer [23] first presented his paper on the technic and indications for aseptic nephro-ureterectomy in 1921. He and his staff had performed 40 such operations without any operative mortality; this suggested that the added risk of removing the whole ureter through the second pararectus incision is negligible.

The technic of the operation has not been changed. The kidney is freed, and its vascular pedicle is carefully tied and cut across, leaving the kidney attached to the ureter. The ureter is then freed, the hand being insinuated retroperitoneally, with great care, well below the iliac vessels, which can always be recognized by the pulsation. If care is not exercised, it is conceivable that the peritoneum, particularly if unusually adherent, may be inadvertently torn. It is also necessary to adhere closely to the ureter, proceeding gradually as the periureteral adhesions are bluntly separated with the fingers. When the ureter has been separated well down into the pelvis in this manner, it is tied with a heavy silk traction ligature, which lies on the patient's abdomen, and the devascularized kidney is replaced in the wound and covered with packing gauze. The patient is then rolled partly on his back so as to expose the iliac fossa and the region for the incision and the exposure of the ureter. An extraperitoneal avascular pararectus incision through the sheath of the rectus muscle is used for the approach to the ureter. No muscles are cut. The rectus muscle is pulled mesially, and the retroperitoneal space is rapidly entered. By traction on the silk ligature attached to the ureter, this structure is easily identified, hooked up and freed from the bladder as well as upward, so as to liberate it in its entire course. The kidney can then be exposed, and by drawing on the silk traction ligature, the kidney and the attached ureter, ligated at its lower end and unopened, are readily lifted out of the lumbar wound. Both incisions are closed in layers, with as little rubber dam drainage as possible.

Beer stated that the indications for complete aseptic nephro-ureterectomy are not often encountered, as may be noted by the fact that he has performed only 40 such operations in more than twelve years in a rather active service for patients with renal diseases. The three main indications for this operation are as follows: (1) papillary growths of the renal pelvis or ureter (4 cases); (2) tuberculosis of the kidney with marked stricture at the lower end of the ureter, associated with a large, dilated, very thickened or thinned ureter (empyema) (24 cases), and (3) hydro-ureteronephrosis or pyo-ureteronephrosis caused by intrinsic or extrinsic stricture at the lower end of the ureter, by a firmly impacted stone or by a unilateral dilated ureteral orifice (2 cases).

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23. Beer, Edwin: Further Experience with Aseptic Nephro-Ureterectomy, J. Urol. **29**:135 (Feb.) 1933.

Infection.—Kindall [24] reported a case of pyelitis cystica and ureteritis cystica diagnosed by urography and confirmed at operation; so far as can be determined by a study of the literature, this is the first case conclusively diagnosed. Cystoscopy was not of diagnostic value since the bladder was not involved. The ureters were dilated because of obstruction of their lumens by the cysts, mechanically causing back pressure or interference with the peristalsis of the ureter.

Kindall suggested a method of treatment: Large ureteral catheters passed to the renal pelvis and left in place for several days may cause mechanical rupture of many cysts, and the injection of a solution of silver nitrate when the catheters are removed, by its astringent action, may destroy other traumatized cysts.

URETER

Tumor.—Spampinato [25] reviewed 88 cases of primary tumor of the ureter from the literature and added a case of his own. These rare tumors appear to owe their origin to some form of mechanical irritation, which is not infrequently furnished by the presence of calculi. The calculi themselves may, however, be secondary, resulting from urinary stasis with decomposition of urine, such as occurs in cases of disease of the prostate gland, or forming around coagulations of blood. Persons of both sexes are equally affected. The age of greatest incidence is between 50 and 60, but cases have been observed among patients aged from 32 to 80. The tumors may be of connective tissue, of epithelial tissue or of a combination of the two. They may be benign or malignant. Opinions differ as to which of these classes predominates, some authors having observed more malignant growths and others more benign growths in the ureter. Papillary carcinomas are more common than nonpapillary ones. There is a tendency to believe that when papillomas of the ureter are multiple they should be regarded as malignant from the outset.

The effect of the tumor on the remainder of the ureter and on the kidney is to cause an obstacle to the outflow of urine, resulting in urinary stasis with consequent dilatation above the point of obstruction. The walls of the ureter become greatly thickened and may even resemble a loop of intestine. As a result of exaggeration of its length the ureter becomes tortuous and describes long spirals. The dilatation is greatest in tumors situated low in the ureters and in those of long duration. The content may be urine alone (hydro-ureter) or urine mixed with blood

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24. Kindall, Lloyd: Pyelitis Cystica and Ureteritis Cystica, J. Urol. **29**:645 (June) 1933.

25. Spampinato, Carmelo: Tumori primitivi dell'uretere, Arch. ital. di urol. **9**:347 (Oct.) 1932.

(hemato-ureter), or it may become purulent as a result of secondary infection. The renal pelvis dilates and may become hydronephrotic. Metastasis follows either the lymphatic or the hematic route. Sometimes the retroperitoneal lymph nodes are infiltrated, with secondary carcinomatous development. Metastasis may also find its way to various organs of the body, and local diffusion may occur into the bladder, rectum, vagina, iliac bones or iliac vessels. The tumors vary in size from that of a walnut to that of a lemon, or they may even be much larger, especially if the growth is sarcomatous. They occur more often in the lower part of the ureter and more often in the right ureter than in the left.

The three principal symptoms are hematuria, pain and tumefaction. These are not pathognomonic, however, and there is no unanimity of opinion as to which predominates or as to the type of pain, which differs widely in individual cases. The differential diagnosis from renal tumor is very difficult because of the similarity of the symptoms. Cystoscopy is sometimes decisive, for example, when it reveals a neoplastic plug protruding constantly or intermittently into the bladder from a ureteral meatus. In 40 per cent of the cases the condition is diagnosed at operation or after death. Various erroneous diagnoses have been made, such as iliac sarcoma, ureteral calculus, vesical papilloma or tumor of the kidney. If the ureteral catheter meets an obstacle, calculus should first be thought of, but the obstruction may be a kink or a tumor. A rule that is more or less sound, but not absolute, is that if during a hemorrhage examination reveals an obstruction without the shadow of a calculus, and if the hemorrhage increases in the course of maneuvers, a tumor of the ureter should be suspected. If a tumor is present, the flow of urine will lack its customary rhythm; atony of the pelvis and ureter causes excretion of the urine drop by drop. If urohematonephrosis is found, it suggests a tumor of the ureter or pelvis. In some cases the catheter may remove a fragment of the tumor. If hematuria and pain persist after nephrectomy, it should be suspected that the ureter is at fault. Since this involves two operations, with loss of time and errors in prognosis, it is of great importance to make the correct diagnosis in advance of operation. When a tumor of the ureter has been diagnosed, the ideal procedure is nephro-ureterectomy in one or two stages. The performance of a more limited operation on the ureter alone in order to cause less trauma is not a sound practice in view of the fact that the renal function is often diminished when there is a tumor of the ureter (hydronephrosis, secondary infection, pyonephrosis), which demands removal of the kidney as well. In addition, there is the possibility that a tumor appearing in the ureter may in reality be secondary to a tumor of the kidney or of the pelvis.

Stone.—Ravich [26] reported 758 cases of ureteral stones, 529 (69.8 per cent) of which occurred among males, and 229 (30.2 per cent) among females. There were 685 cases of single and 73 of multiple stones. Three hundred and forty-two patients had ureteral calculi on the right side, 404 on the left side and 12 on both sides. In 684 cases roentgenograms gave positive evidence of stones, and in 74 cases the results were negative. In 54 of the cases in which the results of roentgen examination were negative a scratch on the wax tip of the catheter indicated the presence of a stone. In 8 of the remaining 20 cases, stones were found projecting from the ureteral meatus; in 2 cases the diagnosis was arrived at from the appearance of the orifice; in 1 case a defect in filling was apparent in the urogram, and in 9 cases stones were found free in the bladder. At times the grating noted on withdrawal of the catheter assisted in making the diagnosis. In Ravich's practice the wax-tipped catheter was as important in making the diagnosis as were roentgenograms, and in the presence of stones composed of uric acid the use of the catheter was often the only measure whereby a diagnosis could be made.

Manipulative cystoscopic measures were necessary in most of the cases in this series. With these procedures Ravich included: the simple passage of a ureteral catheter to dislodge the stone; dilatation of the ureter by indwelling single or multiple catheters or by ureteral bougies; extraction by means of a stone dislodger of stones impacted within the ureteral orifice or the intramural portion of the ureter; enlargement of the ureteral orifice either by an electric cutting current or by scissors, and finally, lithotripsy of a growing vesical stone by his lithotriptoscope. In the remaining cases the stones either were passed spontaneously or required open operation. In 48 cases the calculus was passed spontaneously; in 456 it was passed after the simpler cystoscopic manipulations; in 37 it was extracted from the ureteral orifice, and in 20 it was found in the bladder and extracted.

Ravich stated that urinary stasis seems to be the only constant factor necessary for the formation of a stone in the urinary passages. The chemical character of the stone seems to depend on the hydrogen ion concentration of the urine, which may change from time to time and thus accounts for the different laminae so often demonstrated in stones. Calculi seem to form when as a result of urinary stagnation some change occurs in the secretory function of the tubular epithelium, causing coalescence or diminution of the protective colloids and consequent precipitation of the unattached crystalloids. Trauma, faulty diet, infection and foreign bodies are often contributory causative factors in the presence of stasis.

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26. Ravich, A.: Critical Study of Ureteral Calculi, J. Urol. **29**:171 (Feb.) 1933.

The fact that ureteral calculi occur twice as frequently among males as among females, and the 80 per cent incidence among adults aged from 21 to 50 correspond with the incidence of inflammatory conditions of the adnexa. This is borne out by the fact that in the 393 examinations of the prostate gland recorded, only 82 men (21 per cent) had what appeared to be normal prostate glands and seminal vesicles; the remainder revealed some degree of recognizable pathologic change. The passage of ureteral stones is hindered by physiologic narrowings, kinks, strictures, fixation of the ureter and atony of the ureteral musculature.

Spasm.—Samaan [27] made a comparative study of the action of the antispasmodic drugs papaverine, atropine and "visammin" on the intestine and the virgin uterus of the rabbit, on the ureter of the bull and of man and on the fundus of the dog's bladder. He found that these drugs do not influence the tissues to the same degree and under the same conditions of spasm.

Preparations of the tissues were stimulated by barium chloride, which acts directly on plain muscle tissue and contracts it, and by arecaline hydrobromide, which causes contraction by stimulation of the parasympathetic nerve endings in plain muscle tissue. In addition, "ammi visnaga" was used clinically on patients with impacted ureteral calculi.

It was found that atropine relaxes the intestine and the virgin uterus of the rabbit, the ureter of the bull and of man and the dog's bladder if they are made spasmodic through stimulation of the parasympathetic nerves; it fails to relax these organs if the cause of the spasm is directly muscular. For the bladder or the uterus, visammin and papaverine are of practically equal value in causing relaxation. Relaxation results when the spasm is mediated through the nerve, through the muscle or through both. Both papaverine and visammin relax plain muscle tissue by direct action. In the same concentrations papaverine is more effective than visammin on the intestine, whereas the contrary is true for the ureter of the bull and for that of man. This renders visammin superior to papaverine in the treatment of spasm of the ureter and of ureteral stone. Relaxation results when the spasm is mediated through the nerve, through the muscle or through both.

Clinical evidence of the therapeutic value of ammi visnaga in relaxing the ureter of man and thus allowing an impacted ureteral stone of suitable size to pass out through the natural passage or to descend to the bladder is presented.

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27. Samaan, Karam: The Pharmacological Basis of Drug Treatment of Spasm of the Ureter or Bladder and of Ureteral Stone, Brit. J. Urol. **5**:213 (Sept.) 1933.

BLADDER

Tumor.—Geisinger [28] stated that the entire group of nonepithelial tumors comprises only 10 per cent of all vesical neoplasms, and that when the adenomas, sarcomas, angiomas, lipomas and embryomas are excluded from consideration, the field obviously becomes very much narrowed. In all, perhaps 50 cases of fibrous or muscular tumors of the bladder have been reported in the literature.

In view of the fact that the muscular tumors of the bladder often do not produce symptoms and are discovered only at necropsy, it is probable that they occur more commonly than this statement indicates. Although they may occur in any situation, fibromas or myomas are generally found on the trigon or on the posterior wall of the bladder. They may be submucous, pushing into the vesical cavity, sometimes with a long pedicle; interstitial, corresponding to an intramural fibroid of the uterus, or peripheral, projecting into the perivesical tissues or the peritoneal cavity. Histologically, the pure fibromas may be hard and slightly vascular or soft and highly vascular. In either case they are composed essentially of interlacing bands of fibrous tissue. Smooth muscle cells may or may not be intermixed to a varying extent, and the blood vessels may be greatly dilated. The growths are usually sharply demarcated, and there is no true infiltration of the vesical wall. They are typically benign, but malignant degeneration may occur in rare instances. Calcification, fatty changes or necrosis may be present, especially in the hard fibromas on account of their poor blood supply.

There may be no symptoms. When the tumor is submucous it is more likely to give some indication of its presence at an earlier stage, although this type of growth also may exist for a long time without disturbing the patient. Involvement of the ureteral orifice will cause obstructive symptoms referable to the corresponding limb of the upper part of the urinary tract.

Geisinger concluded that the treatment should be surgical. Even if accidentally discovered, the tumors should be removed. Subsequent growth may produce marked symptoms, and though malignant degeneration is rare, there is a definite danger of its development.

Barringer [29] stated that hematuria is a diagnostic symptom of tumors of the genito-urinary tract. He expressed the belief, moreover, that after irradiation of, and presumably after operation on, vesical tumors, hematuria is an important symptom. He stated that in 75 per cent

28. Geisinger, J.: Fibroids of the Urinary Bladder, J. Urol. **29**:661 (June) 1933.

29. Barringer, B. S., in discussion on Rathbun, N. P: Hematuria, J. Urol. **30**:23 (July) 1933.

of his cases in which irradiation was carefully carried out and bleeding occurred afterward, hematuria indicated that he did not have control of the tumor, and the growth recurred.

Coffey [30] reported 11 cases of cystectomy for carcinoma of the bladder. There were 3 deaths as a result of the operation—a mortality rate of 27.27 per cent. In 2 cases in which the operation was performed in two stages on women (first, ureteral transplantation, and second, cystectomy), the patients were alive and well. Two women who had far advanced carcinoma of the bladder which had been treated on numerous occasions by irradiation and fulguration died as a result of an attempt to perform transplantation and cystectomy at one time. In 1 of these cases it was unwise to operate at all. The difficulties encountered in these 2 cases revealed special problems which indicate that the combined operation is unpractical for women even if the condition is favorable for operation. Cystectomy was performed on 7 men with transplantation of the ureters at the same operation. There was 1 death —a mortality rate of 14.28 per cent. Five men were alive and well, and all had been seen or heard from within a month of the presentation of Coffey's paper. All had been examined within five months. Therefore, Coffey stated that 7 were symptomatically cured without evidence of recurrence following cystectomy for carcinoma of the bladder. Aside from being perfectly well and comfortable, these patients were unusually happy and well satisfied with the results, as contrasted with patients afflicted with carcinoma of the rectum, who are often more or less morbid because of the inconvenience of a colonic stoma.

Coffey stated that these results compare favorably with the results of treatment of carcinoma in any other part of the body. In fact, this limited experience, together with the knowledge that as a rule carcinoma of the bladder remains a local process for a long time before it metastasizes, leads to the hope that carcinoma of the bladder may yet be the most curable of all carcinomas which invade the body and that, with added experience, the operation when performed at an early stage of the disease will be no more formidable than any of the other major operations for internal carcinoma.

Coffey concluded that cystectomy for carcinoma of the bladder is probably one of the most successful operations that has been introduced for the treatment of carcinoma, for the reason that diagnosis is made early in the course of the disease whereas metastasis is late, and that with added experience the mortality rate undoubtedly will be low and the percentage of cures high. An essential part of the operation is transplantation of the ureters into the large intestine. This, to be successful,

30. Coffey, R. C.: Cystectomy for Carcinoma of the Bladder, Am. J. Surg. 20:254 (May) 1933.

must be performed by the submucous method of implantation. The author proposed three principles of technic for its performance. The first method may be eliminated immediately. The third method, because of its simplicity, may be favored by some surgeons for the early stages of carcinoma of the bladder, in which the element of time is not important. For the same reason, it may encourage the performance of a radical operation early in the disease, as is done for carcinoma in other parts of the body. The chief criticism is that two operations are required for transplantation of the ureters. The second method is ideal for use in conjunction with cystectomy for carcinoma of the bladder because the two ureters are transplanted in one operation. In men, cystectomy is performed at the same time that the ureters are transplanted, with little, if any, additional risk. The objection is that special skill in the performance of intraperitoneal operations is required.

Smith and Mintz [31] studied 150 cases of tumor of the bladder with regard to age, symptoms, type of tumor, treatment and end-results. They analyzed 37 cases at necropsy as to the type and grade of carcinoma, the presence and distribution of metastasis and the existence of other pathologic conditions.

The authors stated that the grade of malignancy of carcinoma of the bladder has no demonstrable relation to its tendency to metastasize. Squamous-cell carcinomas metastasize almost twice as frequently as papillary carcinomas. One important cause of the poor results of operations for carcinoma of the bladder is the long delay between the occurrence of the first symptom and the patient's entrance into the hospital. A comparison of the results of treatment by resection, by electrocoagulation and by implantation of radium showed that the lowest number of deaths in the hospital occurred among patients treated by electrocoagulation (26 per cent), the next lowest number among patients treated by resection (32 per cent) and the highest number among patients treated by implantation of radium (41 per cent). The end-results of these three methods are approximately the same. The authors expressed the belief that no one method is suitable for all types of carcinoma. The surgeon should be prepared to employ whichever method seems best suited to the individual case.

31. Smith, G. G., and Mintz, E. R.: Bladder Tumor, Am. J. Surg. **20**:54 (April) 1933.

(To be Concluded)